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GLANDULAR FEVER: A FIELD STUDY*

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Ever since Emil Pfeiffer's description in 1889 of the clinical entity glandular fever, this disease, with its negligible mortality and low morbidity, has continued to present a variety of intriguing and unresolved problems.

The purpose behind the present field study was to add to the knowledge of the relationship between the clinical course of the disease and the appearance, duration, and regression of the serological and haematological abnormalities which to-day are considered to provide the laboratory confirmation of a clinical diagnosis. It was hoped that light would be thrown upon the epidemiology, infectivity, incubation period, and possibly upon the process of dissemination.

The field study, lasting for 30 months (July, 1954, to December, 1956), was carried out in the Oxford area normally served by the United Oxford Hospitals, comprising Oxford City, Oxford County, and a portion of North Berkshire. Each general practitioner in this area was invited to notify the Pathological Laboratory of the Radcliffe Infirmary of any suspected case of glandular fever. A pathologist then visited to take blood samples from the patient and any immediate contacts. In all, 1,156 individuals were examined, of whom 498 were suspected on clinical grounds to be cases of glandular fever and 658 were contacts.

Every case in which serological or haematological findings were regarded as significant or suspicious was followed up and the investigations were repeated at intervals of time, which were to some extent dictated by administrative and executive difficulties and the co-operation of the patients. Whenever possible the case was followed until all serological and haematological abnormalities had disappeared. This ideal was realized in only about 25% of cases, largely because clinical recovery and resumption of work often preceded the vanishing-point of the blood changes by many weeks or even months.

Methods

The laboratory investigations in every case included the Paul–Bunnell test and the examination of a blood film, and in most cases a white-cell count.

Paul–Bunnell tests were carried out by a modification of Barrett's (1941) technique. Three separate volumes of each serum are mixed respectively with 4 volumes of saline, 4 volumes of guinea-pig kidney suspension, and 4 volumes of ox-cell suspension, allowed to stand for one hour, and then centrifuged to obtain clear supernatant samples. A "screening test" is then carried out by adding to 0.25 ml. of the kidney-absorbed serum an equal volume of sheep-cell suspension, centrifuging at low speed, and examining the sedimented cells by eye for agglutination. The absence of agglutination is reported as negative; just perceptible agglutination is reported as "doubtful positive, too weak to titrate," and subsequent investigation has shown that this corresponds to a titre of 1:40 after absorption with guinea-pig kidney. If there is obvious agglutination in the screening test a titration is carried out as follows: doubling dilutions of the saline-diluted and absorbed serum are made; an equal volume of sheep-cell suspension is added to each: the mixtures are incubated for one hour at 37° C., allowed to stand at room temperature for half an hour, and then centrifuged at low speed and examined. The highest titre showing agglutination is recorded. Paul–Bunnell reaction is recorded as positive when a serum has a titre of 1:80 or more after absorption with guinea-pig kidney and shows a reduction in titre of at least two tubes after absorption with ox cells.

White-cell Count.—The white cells were counted using a $\frac{1}{6}$-in. (4 mm.) objective and Fuchs–Rosenthal counting chamber. In these circumstances it is possible to make a total count of white cells and at the same time differentiate between polymorphonuclear leucocytes and mononuclear cells (lymphocytes, monocytes, and atypical cells). The absolute counts of mononuclear cells referred to in this investigation were derived in this manner and not by the conventional differential counting method.

Assessment of Abnormal Cells.—The cells which are found in films of the blood of patients with glandular fever are characterized by their variable morphology. In most cases cells belonging to one or more of the three types described by Downey and McKinlay (1923) are found. They vary from cells resembling large lymphocytes to large cells with dark-blue cytoplasm, many of which have nucleoli. In this investigation these cells are referred to collectively as "glandular fever cells" (G.F.

*This field study was undertaken in July, 1954, under the aegis of a committee consisting of Dr. A. M. Cooke and Dr. F. G. Hobson, consulting physicians; Dr. Victoria Smallpeice, consulting paediatrician; Dr. A. H. T. Robb-Smith, director of pathology; Dr. R. G. Macfarlane, clinical pathologist; Dr. J. F. Warin, Dr. T. Anderson, Dr. A. J. Campbell, Dr. N. C. Parfitt, and Dr. H. A. McKenzie-Wintle, medical officers of health for Oxford City, Oxford County, and North Berkshire; Dr. F. Bevan, Dr. A. W. Henderson, and Dr. C. Stringfellow, general practitioners. Secretaries: Dr. Barbara Lawson, 1954–5, and Dr. Mary Wigfield, 1956–7.

cells). No attempt was made to count these cells as a proportion of the total white cells, but each slide was examined carefully, and, from a subjective opinion, the slides on which G.F. cells were found were divided into categories as follows: (1) G.F. cells numerous; (2) G.F. cells present in moderate numbers, both these being reported as haematologically positive (Haem.+); and (3) occasional G.F. cells.

Results

The individuals examined can be conveniently considered in four groups on the basis of the laboratory findings.

Group 1: 242 cases were Paul–Bunnell positive (P.B.+). Group 2: 100 cases were Paul–Bunnell negative (P.B.−) but haematologically positive (Haem.+). In each of these groups G.F. cells were reported "numerous or present in moderate numbers." The symptomatology and clinical findings of the cases in these two groups were found to be very closely comparable, and are considered later.

Group 3: 99 cases were P.B.−, haematologically doubtful—that is, G.F. cells "occasional"; 43 cases were asymptomatic, and 56 showed clinical symptoms or signs possibly compatible with a diagnosis of glandular fever, though it is recognized that many diseases can mimic the clinical manifestations of glandular fever and that "occasional G.F. cells" are reported in many diseases, usually those of viral origin. An alternative diagnosis to the provisional diagnosis of glandular fever was in some cases established later.

Group 4: 715 cases were P.B.−, haematologically normal. This group consisted of asymptomatic contacts and clinically suspect cases with completely negative laboratory findings.

The 814 cases in groups 3 and 4 are excluded, therefore, from further consideration.

Group 1 and Group 2 Cases

The cases in groups 1 and 2 are compared and contrasted. Each of these 342 cases was provisionally regarded as a case of glandular fever; although the follow-up of group 2 cases was less consistent and determined than that of group 1 cases, it was invariably proceeded with in the reasonable expectation that a positive Paul–Bunnell reaction would develop.

Clinical Course

There was no fatal case in the whole series. The clinical features were recorded by two independent clinical observers, the general practitioner in charge of the case and the visiting pathologist, and did not rest upon the clinical observations of one individual. No new clinical facts emerged relating to symptoms and signs which have not been previously reported in the literature of glandular fever.

TABLE I.—*Incidence and Priority of Symptoms and Signs*

Symptoms and Signs	Group 1 (242 Cases) P.B.+ (%)	Priority	Group 2 (100 Cases) P.B.− Haem.+ (%)	Priority
Enlarged lymph nodes	88	1	80	1
Sore throat	80	2	54	3
Pyrexia	75	3	69	2
Malaise	52	4	46	4
Headache	47·5	5	44	5
Palpable spleen	26	6	14	8
Abdominal symptoms	18	7	25	6
Anorexia	17·5	8	14	8
Ocular	15·5	9	11	9
Rashes	15·5	9	22	7
Stiff neck	11	10	6	11
Myalgia	10	11	9	10
Coryza	7·5	12	11	9
Enlarged liver	5·5	13	2	12
Icterus	5	14	1	13
Nephritis	1	15	0	

Table I shows the percentage incidence and priority of symptoms and signs in the two groups. The close parallelism between the main symptoms and signs was such that on purely clinical grounds it was impossible to distinguish group 1 and group 2 cases in the active disease state.

The clinical course of the disease, however, in the group 2 cases appeared generally to be less severe and recovery more speedy. This clinical observation was supported by the fact that during the 30 months of this field study there were admitted to the Radcliffe Infirmary, Oxford, or to the Slade Fever Hospital, Oxford, 79 patients, of whom, after investigation, 70 were found to be group 1 and 9 group 2.

The grounds for admission were acute illness for diagnosis and investigation (mainly to the Radcliffe Infirmary) or acute illness which for social or domestic reasons could not be treated at home (mainly to the Slade Hospital).

TABLE II

Treated	Group 1	Group 2	Total
Radcliffe Infirmary	18	4	22
Slade Hospital	52	5	57
Hospital total	70	9	79
At home	172	91	263
Total	242	100	342

Table II shows the place of treatment. In 67 of the hospital patients (85%) the illness followed an uneventful course rarely exceeding 10 days' stay; 12 (15%) presented with worrying or unusual clinical features, although each of the 79 ultimately made a complete clinical recovery. The remaining 263 patients (172 group 1, 91 group 2) were treated in their homes by their general practitioners, the disease following an uneventful course with complete clinical recovery.

Summary of 12 Unusual Cases

All 12 patients presenting with worrying or unusual clinical features were group 1 cases (5%); brief details are given below.

Radcliffe Infirmary

Case 1.—Man aged 23. Presenting symptom—haematemesis and abdominal pain.

Case 2.—Man aged 21. A known haemophiliac under treatment (including multiple transfusions) for a retroperitoneal haematoma with complications developed an attack of glandular fever while in hospital.

Case 3.—Man aged 30. Acute onset with rigors, headache, vomiting, and delirious on admission. C.S.F. normal.

Case 4.—Girl aged 7. Admitted with dysphagia and respiratory obstruction secondary to a severe anginose attack with cervical adenitis and superimposed infection with *Candida albicans*.

Case 5.—Man aged 23. Severe hepatitis, sequel to an attack of glandular fever.

Case 6.—Boy aged 7. Persistent fever, erythematous rash, epistaxis, and hepatitis.

Case 7.—Girl aged 5. Pyrexia, drowsiness, vomiting, and periorbital oedema with transient albuminuria and impairment of renal function.

Case 8.—Man aged 24. Tonsillitis, cervical adenitis, papular rash with petechiae, thrombocytopenia, and nephritis.

Case 9.—Woman aged 20. Known and controlled diabetic—temporary disturbance of control of diabetes—afebrile.

Slade Hospital

Case 1.—Girl aged 18. Jaundice and menorrhagia.

Case 2.—Man aged 24. Jaundice.

Case 3.—Man aged 39. Very severe and protracted jaundice and hepatitis.

Yearly Trend and Seasonal Incidence

The yearly trend and seasonal incidence in groups 1 and 2 are shown in Table III. In each of the two complete years (1955 and 1956) there was a marked increase in group 1

cases in April, May, June, and July. Group 2 cases showed no such regular seasonal incidence. In 1954 there was a rise in August, the explanation of which was not obvious. In 1955 there was a rise in November, equally inexplicable. In 1956 there was a rise in July, which was directly attributable to an identified "epidemic" in an Army hospital.

TABLE III.—*Seasonal Incidence*

	Group 1 (242)			Group 2 (100)		
	1954	1955	1956	1954	1955	1956
January		5	9		3	2
February		4	9		—	3
March		7	5		3	2
April		11	13		2	6
May		13	23		2	3
June		9	11		1	3
July	4	9	10	3	1	16
August	4	6	4	9	2	3
September	7	8	10	—	—	1
October	10	9	8	2	2	5
November	7	8	9	3	12	5
December	3	4	3	5	1	—
Total	35	93	114	22	29	49

Incidence Related to Sex and Age

The age and sex distribution of groups 1 and 2 are shown in Table IV. In group 1 the age incidence rises sharply to a peak in the decade 20–29, after which it falls even more sharply, whereas in group 2 the peak incidence is in the decade 0–9, with a steady fall thereafter.

TABLE IV.—*Age and Sex Incidence*

Age	Group 1 P.B.+			Group 2 P.B.− Haem.+		
	M	F	Total	M	F	Total
0–9	13	6	19	26	12	38
10–19	21	56	77	19	5	24
20–29	85	36	121	12	8	20
30–39	5	7	12	6	4	10
40–49	2	3	5	1	—	1
50–59	2	2	4	1	—	1
60+	—	—	—	—	—	—
Not known	1	3	4	2	4	6
Total	129	113	242	67	33	100

There is an almost equal distribution between the two sexes in group 1 over the whole range, whereas in group 2 the male:female ratio is 2:1.

In group 1 there is a higher incidence in females in the decade 10–19, which is reversed in the decade 20–29, whereas in group 2 the incidence in males is greater over the whole age range.

In view of the facts that Oxford is a university city and a regional hospital centre, it seemed possible that the influx of students of both sexes at each term, and the considerable numbers of resident nurses, might influence significantly the seasonal, age, and sex incidence of these two disease states. This was not found to be the case. Complete exclusion of all individuals in the above two categories left the main features of incidence unchanged.

Relation of Laboratory Results to Clinical Course

An objective of the present field study was to follow the serological and haematological changes associated with the active disease state until normality was restored.

As mentioned above, this was achieved in only approximately 25% of cases in groups 1 and 2, for a variety of causes beyond any observer control. Such were lack of co-operation by patients who had clinically recovered from the disease and returned to work, movement of patients attending school or university, emotional distress caused by venepuncture in children, etc. The follow-up was regarded as satisfactory and as providing homogeneous data in this 25% because: (1) it could be confidently considered that the first blood samples had been taken within 14 days of "the onset of symptoms," an event which can be in doubt in a proportion of cases; (2) subsequent examinations had followed at intervals of less than six weeks; in practice, the interval was most usually three to four weeks.

A considerable body of data was also provided by the 75% of cases failing to qualify as above, which nevertheless helped to fill in some details of the pathological and clinical pictures.

A. Paul–Bunnell Test

The technique employed for this test has been described above, along with the system of reporting as positive, doubtful positive too weak to titrate, and negative.

Conversion of P.B.− to P.B.+.—Eleven cases with clinical symptoms and signs showed on the first examination a negative reaction which subsequently became positive. In three cases the date of onset of clinical symptoms was uncertain; in eight cases it could be definitely fixed (see Table V). These eight cases illustrate

TABLE V

Case	Days from Onset	P.B.	G.F. Cells	Days from Onset	P.B.	G.F. Cells
1	1	−	+	16	+	−
2	4	−	+	12	+	+
3	4	−	+	22	+	−
4	7	−	+	16	+	+
5	7	−	+	21	+	+
6	13	−	+	21	+	+
7	18	−	+	41	+	Occasional
8	47	−	+	89	+	−

G.F. cells + = Numerous or moderate. G.F. cells − = None.

several other points: (*a*) Cases 1–5 had G.F. cells in significant numbers within one week of the onset of symptoms. (*b*) Cases 1 and 3 show that in rare instances *all G.F. cells have disappeared* from the peripheral blood film by the third week from onset of symptoms, the Paul–Bunnell reaction now being positive. (*c*) In Case 7 the "occasional G.F. cells" present six weeks from the onset of symptoms may be significant in conjunction with a P.B.+ test indicating a group 1 case. (*d*) Case 8 illustrates a long delay before the Paul–Bunnell reaction became positive (89 days), all G.F. cells having by now disappeared from the peripheral blood film, although present in significant numbers at 47 days.

Conversion of Doubtful Positive P.B.(+) to P.B.+.—Six cases showing P.B.(+) later became P.B.+, each being haematologically positive (G.F. cells numerous or moderate) both on the first and subsequent examination, and each with clinical symptoms and signs. Details are shown in Table VI.

TABLE VI

Case	Days from Onset	P.B.	G.F. Cells	Days from Onset	P.B.	G.F. Cells
1	3	(+)	+	8	+	+
2	7	(+)	+	15	+	+
3	11	(+)	+	20	+	+
4	11	(+)	+	20	+	+
5	14	(+)	+	40	+	+
6	26	(+)	+	39	+	+

P.B.(+) = Paul–Bunnell doubtful positive, too weak to titrate.
G.F. cells + = Numerous or moderate numbers.

Reversion of P.B.+ to P.B.(+).—Of 222 cases fully confirmed on the basis of serological (P.B.+), haematological, and clinical evidence, 51 were found to yield a P.B.(+) on average three months after the onset of the disease, when they were asymptomatic. Thus in 57 cases the evidence was absolute that a serum showing a just perceptible agglutination reported as "doubtful positive, too weak to titrate" was significant and indicated that in a group 1 case the disease was either in the course of development or, much more often, that the disease had passed its peak and the serological finding was returning to normal, although many weeks or months after the active clinical manifestations of disease had disappeared. Twenty cases

were found to yield P.B. (+) which could not be followed either to a positive conversion or to a return to normal. Of these, 14 showed symptoms or signs compatible with glandular fever (9 showed G.F. cells numerous or moderate, 5 showed normal films). The remaining 6 had no symptoms and a normal blood film, but all had been intimate contacts of group 1 cases. These 20 cases have been included in the total of 242 P.B.+ cases.

First Appearance of P.B.+.—The onset of clinical symptoms can rarely be precisely dated, and laboratory investigations were undertaken as and when requested, but in 205 cases where the date of onset of clinical symptoms could be judged with reasonable certainty a P.B.+ was obtained on the first examination—in 69% of cases by the 14th day, in 90% by the 21st day, and in 94% by the 28th day.

TABLE VII.—*Duration of Paul-Bunnell Reaction*

Time in Weeks from Onset	Group 1 (P.B.+ Haem.+) 59 Cases P.B.+	% P.B.+	66 Cases Haem.+	% Haem.+	Group 2 (P.B.− Haem.+) 34 Cases Haem.+	% Haem.+
<2	59	100	66	100	34	100
2	57	97	65	99	24	71
3	56	95	59	89	22	65
4			55	83	15	44
5	53	90	44	67	8	24
6	51	88	33	50	3	9
7	47	80	23	35	2	6
8	45	76	17	26	0	0
9	38	64	11	17		
10	35	59	7	11		
11	28	47	4	6		
12	25	42	3	5		
13	22	37	2	3		
14	20	34	2	3		
15	16	27	1	2		
16	15	25	1	2		
17	13	22	1	2		
18	11	19	1	2		
19			0	0		
20	10	17				
21	8	14				
22						
23	6	10				
24	5	8				
25	3	5				
27	2	3				
33	1	2				
38	0	0				

TABLE VIII.—*Shortest and Longest Duration of Positive Paul-Bunnell Reaction from Onset*

	Two Shortest Cases: Time from Onset	Report		Three Longest Cases: Time from Onset	Report
Case 1	5 days	P.B.+	Case A	11 days	P.B.+
	14 ,,	P.B.−		38 weeks	P.B.(+)
,, 2	2 ,,	P.B.+	,, B	16 days	P.B.+
	16 ,,	P.B.(+)		63 weeks	P.B.+
			,, C	18 days	P.B.+
				34 weeks	P.B.+

Reversion of P.B.+ to P.B.−.—In 59 cases the Paul-Bunnell reaction was positive within two weeks of the onset of symptoms and was followed up systematically to the point of reversion to negative (Table VII). The interval between tests in no case exceeded six weeks, and averaged between three and four weeks. Case A (Table VIII) was followed at monthly intervals; in Cases B and C the follow-up was not regular, so that the possibility of relapse and/or reinfection could not be excluded. (*Note:* One case followed by serial tests, from the onset of clinical symptoms, showed a strongly positive Paul-Bunnell reaction (Haem.+), with steady fall of titre to *negative* six months later. Then, eight months after the original illness, symptoms and signs recurred and the Paul-Bunnell reaction again became positive. ? Relapse. ? Reinfection.)

B, White-cell Count and G.F. Cells

White-cell Count.—Table IX contrasts the white-cell counts obtained in group 1 cases with those of group 2 as regards both an *absolute* increase of mononuclears—that is, 3,000 per c.mm. or more—and a *relative* increase of mononuclears—that is, 50% or more. It will be seen that group 1, as compared with group 2, has a higher percentage of cases with both an *absolute* and a *relative* increase of mononuclears.

TABLE IX.—*Mononuclear Counts*

Absolute increase (i.e., mononuclears 3,000 or more in first and/or subsequen counts)

	No. with Monos 3,000 or More	No. with Monos Under 3,000	No. in which Counts were Done	No. with No Detailed Differential Count	Approx. % of Cases Examined with Monos 3,000 or More
Group 1 ..	189	13	202	40	94
,, 2 ..	68	18	86	14	79

Relative increase (i.e., mononuclears 50% or more in first and/or subsequent counts)

	No. with Monos 50% or More	No. with Monos Less than 50%	No. in which Counts were Done	No. with No Detailed Differential Count	Approx. % of Cases Examined with Monos 50% or More
Group 1 ..	179	15	194	48	92
,, 2 ..	62	24	86	14	72

G.F. Cells

Direct comparison of the blood films of group 1 and group 2 cases requires some qualification, because in seropositive cases the evidence of a positive Paul-Bunnell reaction clearly indicates that the case could well be a group 1 case in a regressive phase as regards G.F. cells, which in an average case disappear many weeks before the Paul-Bunnell test reverts to normal.

"G.F. cells present, numerous or in moderate numbers" has been taken as the essentially *positive* report, abbreviated in tables and graphs as "Haem.+"

"G.F. cells occasional or very infrequent" has been taken as an essentially *negative* report. Such a report, however, was returned on a few cases in definite association with a P.B.+ and/or a fully *positive* blood film on previous or subsequent examinations. In these few cases this finding clearly indicated an incipient or regressive phase of disease group 1 or group 2.

In the absence of previous or subsequent confirmatory serological or haematological evidence, the finding was regarded as excluding group 1 and group 2 disease and indicating a different aetiology.

In group 1 the haematological reports in association with a P.B.+ were as follows: 220 cases, G.F. cells numerous or moderate; 6 cases, G.F. cells occasional; and 16 cases, normal film. In the 22 cases showing G.F. cells occasional or a normal film there was a delay of three to eight weeks in taking the first blood film and often doubt about the date of onset of symptoms. Table VII shows that all G.F. cells disappear from the peripheral blood film in 74% of patients by the eighth week after the onset of symptoms, and may disappear even earlier.

In group 2 there could be no confusion or doubt about the interpretation of the haematological findings, because the diagnosis, by definition, rested simply on the report "G.F. cells present, numerous or in moderate numbers."

Appearance of G.F. Cells

No case was found to be P.B.+ *before* the appearance of G.F. cells, although in regressive phases of the group 1 cases a P.B.+ reaction persisted long *after* all G.F. cells had disappeared.

In most patients the "onset of symptoms" has been rapid, with a prodrome of two to seven days; in a minority the onset has been sudden and could be more precisely dated.

and in a very small number of patients there is evidence to suggest that the onset of the disease state can be so insidious and its clinical course so mild that it passes unnoticed. These observations applied equally to group 1 and group 2 disease, and make it impossible accurately to relate the serological and haematological changes with a precise date.

First Appearance of G.F. Cells.—As was the case with the Paul–Bunnell test, the onset of clinical symptoms can rarely be precisely dated, and laboratory investigations were undertaken as and when requested. G.F. cells were present "numerous or in moderate numbers" on the first examination where the onset of symptoms could be judged with reasonable certainty (Table X).

TABLE X

	No. of Cases	14th Day from Onset	21st Day from Onset	28th Day from Onset
Group 1	206	76%	92%	96%
,, 2	80	84%	91%	99%

In group 1, 36 cases, and in group 2, 20 cases, have been excluded because they were first examined *more than four weeks* from the onset of symptoms or because the date of onset was uncertain.

Disappearance of G.F. Cells

In 66 Haem.+ cases of group 1 and 34 Haem.+ cases of group 2, the first positive finding was recorded within 14 days from the onset of symptoms and the changes were systematically followed to the vanishing point (see Table VII and Fig. 1). The interval between tests in no case exceeded six weeks and averaged between three and four weeks.

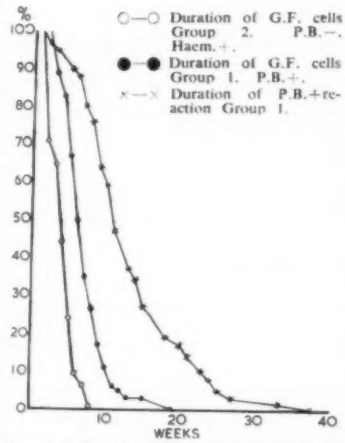

FIG. 1.—Showing disappearance of G.F. cells (see also Table VII).

As defined above, this material is homogeneous, but must not be accepted as representing more than an average picture of the peripheral blood film changes. G.F. cells, however, have been found to disappear earlier and to persist longer than is indicated in Table VII and Fig. 1.

The shortest and longest durations from onset of G.F. cells in blood films are shown in Table XI.

Such findings were rare, but a few cases in each group yielded results showing unusually short or long duration of G.F. cells in the blood film.

TABLE XI

	Time from Onset	Report
Group 1 disease (P.B.+ at all test times)		
Shortest case ..	3 days	G.F. cells in moderate numbers
	12 ,,	Normal film
Longest ,, ..	14 weeks	G.F. cells in moderate numbers
	18 ,,	Normal film
Group 2 disease (P.B.−)		
Shortest ,, ..	2 days	G.F. cells in small numbers
	6 ,,	,, ,, in moderate numbers
	9 ,,	Normal film
Longest ,, ..	6 weeks	G.F. cells in moderate numbers
	8 ,,	Normal film

There were a few cases in which G.F. cells were present in the peripheral blood film for greater periods than shown above (group 1, 18 weeks; group 2, 8 weeks), but in these cases the follow-up had been broken and inconsistent, so that there was a possibility of "relapse," "reinfection," or intercurrent illness having disturbed the final blood picture. If these were included in Table VII, the time limit between the onset of symptoms and the disappearance of G.F. cells would be increased.

Conclusions

From the foregoing data and Table VII and Fig. 1, certain conclusions can reasonably be drawn.

Group 1.—A majority of patients are P.B.+ by the 14th day from the onset—a few are P.B.(+) or P.B.− in this early phase; in each of the observed cases when negative or doubtful reactions were obtained the blood film was diagnostic, the Paul–Bunnell conversion following later.

If the Paul–Bunnell test is followed up, a number of cases will be found to yield a P.B.(+) before the reversion to negative. The P.B.+ findings persist approximately twice as long as the G.F. cells in the peripheral blood film. Clinical recovery will have occurred many weeks, even months, before the Paul–Bunnell reaction reverts to negative.

Group 2.—The peripheral blood film does not distinguish group 1 from group 2 cases. By the 14th day from onset 84% of group 2 cases yielded positive films compared with 76% of group 1 cases, but the G.F. cells in group 2 cases disappeared from the peripheral blood in approximately half the time taken in group 1 cases.

In a few cases of either group 1 or group 2 the G.F. cells may appear or disappear earlier or later than the average times indicated by Table VII and Fig. 1.

In assessing the laboratory findings in any given clinical case, it is obvious that the probable phase of the disease must be taken into account, and that, if the findings are equivocal, the investigations should be repeated.

Epidemiology

A major objective of the present study was to collect evidence of the infectivity, mode of dissemination, and incubation period of glandular fever. The very considerable effort to achieve this objective produced the following results.

Military Hospital, Wheatley

Only one small outbreak of disease was identified that could be considered an "epidemic."

Chronology.—May, 1956: Two cases of glandular fever group 1 were admitted to the hospital and discharged for sick leave in the *last week of May*. *June, 1956: In the last week* the "epidemic" began, involving members of the hospital staff and long-term in-patients in the wards throughout July and the first week of August.

Fig. 2 shows the course of events, and cases can be identified by the numbers. With the Paul–Bunnell test as a yardstick, the cases fall into two groups.

(*a*) *Group 1 Disease* (*P.B.*+).—Three cases, all members of the hospital staff, developed the disease as follows: June 30, No. 2, a nurse; July 20, No. 8, a nurse; August 8, No. 15, a staff sergeant. Cases 2 and 8 were in daily close contact, but neither had any obvious or known contact with Case 15.

(*b*) *Group 2 Disease* (*P.B.*−).—There were 12 cases (10 in members of the hospital staff and 2 in long-stay in-patients). These cases can be subdivided: nurses (Nos. 1 and 3), R.A.M.C. orderlies (Nos. 4, 5, 6, 7, 11, 12, and 13), in-patients (Nos. 9 and 10), and medical officer in charge of patients and wards (No. 14).

As shown in Fig. 2, three further group 2 cases were admitted from outside units (one on July 18, July 19, and August 3) which must be regarded as possible additional

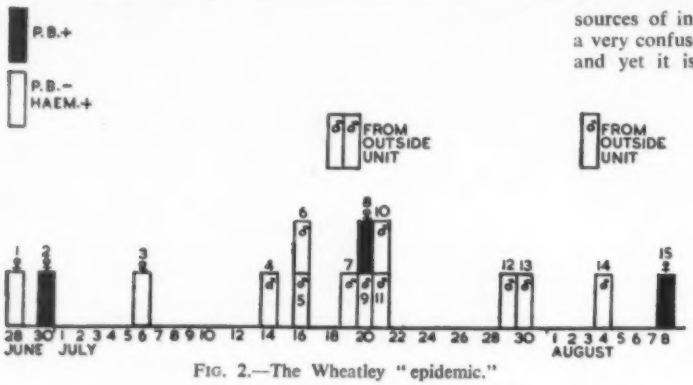

FIG. 2.—The Wheatley "epidemic."

TABLE XII

Case No.	Primary Group I Case	Age	Contacts: No. Examined	Contacts: No. Positive Group I	Weeks after Contact with Primary Case	Notes
1	G.W.	10	3 (family)	1 (M.W.)	1	Brothers: ? shared infection
2	R.T.	9	3 ,,	1 (B.T.)	3	Same household
3	M.H.	16	4 ,,	1 (F.H.)	35	,, ,,
4	J.G.	23	1 (college)	1 (R.H.)	3½	Same flat
5	D.T.	22	1 ,,	1 (N.D.L.)	4	Adjoining room
6	N.D.L.	20	1 ,,	1 (D.P.)	14	Shared ,,
7	S.H.	18	1 (nurse)	1 (E.M.C.)	2	,, duty
8	J.S.	18	2 (nurses)	1 (E.B.) 12; 1 (A.E.H.) 12	12	Simultaneous, shared duty
9	J.M.	25	1 (office)	1 (W.G.G.)	16	Same office room
10	I.S.	24	1 ,,	1 (R.S.)	Uncertain	See note
11	P.H.	24	1 (fiancé)	1 (J.P.)	11½	,, ,,
12	Mrs. S.	30	4 (family)	1 (P.S.); 1 (D.S.)	Uncertain 14	Same household
13	Mr. and Mrs. T.	40	1 ,,	1 (D.T.)	Uncertain	,, ,,
14	G.P.	23	5 ,,	1 (P.P.)	,,	,, ,,
15	G.L.	25	1 (fiancée)	1 (E.E.)	,,	See note ,,

Notes on Cases

Cases 7 and 8.—nurses in the same hospital.
Case 10 (I.S.).—found to be P.B.+, with normal blood film, no history of illness; suspected as source of infection in R.S.
Case 12 (Mrs. S.).—found to be P.B.(+) with normal blood film; no history of illness; suspected as source of infection in P.S. and D.S. (her children).
Case 13 (Mr. and Mrs. T.).—parents of D.T., found to be P.B.(+) with normal blood film; no history of illness; suspected as source of infection in D.T.
Cases 14 and 15.—the contacts P.P. and E.E. were in each case examined 7 weeks after contact with the primary case. Each case was P.B.(+) and the blood films were normal; there was therefore in each case the possibility of a shared common source of infection, the "primary" case experiencing a full-blown clinical attack, the secondary "contact" having a subclinical attack.

TABLE XIII

Case No.	Primary Group I Case	Age	Contacts: No. Examined	Contacts: Group 1	Contacts: Group 2*	Weeks after Contact with Primary Case	Notes
1	M.F.	8	1 (family)	—	1 (B.F.)	15	Same house
2	H.G.	19	1 (nurse); 1 ,,	1 (J.)	1 (J.P.)	3½; 3½	Ward and hospital contacts
3	M.	19	1 (nurse); 1 ,,	1 (H.G.)	1 (M.S.)	12½	Nursed M.
4	B.J.S.	20	1 (P.O.—R.A.F.)		1 (S.)	9 Uncertain	Shared duty ,, room
5	M.H.	24	1 (college)		1 (J.R.)	½	Friends
6	T.T.	21	1 ,,		1 (M.L.)	6	,,
7	W.G.G.	18	1 (fiancée)		1 (W.M.)	Uncertain	,,

* Each of these group 2 cases was followed up for eight to nine weeks; the Paul–Bunnell reaction remained persistently negative.

Notes on Cases

Cases 2 and 3.—all nurses in same hospital.
Case 2.—apparent source of infection for group 1 Case J. and group 2 Case J.P., daily contacts.
Case 4 (B.J.S.).—P.B.+ but normal film; no history of illness; suspected of subclinical attack and source of infection for S.
Case 7 (W.G.G.).—an office contact of Case 9 (J.M.), in Table XII; circumstances as regards fiancée W.M. difficult to interpret, as her clinical disease (group 2) started six days prior to W.G.G.'s illness.

sources of infection. In summary, the "epidemic" shows a very confused picture with no very obvious attack pattern, and yet it is difficult to exclude an association between group 1 and group 2 cases. Alternatively, it could be maintained that two separate diseases were associated coincidently in one hospital unit—group 1 cases with an incubation period of about 20 days, group 2 cases with an incubation period of five to eight days.

Other Examples of Associated Infection

Additional to the Wheatley Hospital "epidemic," there were a number of cases of disease in individuals associated by family, social, and occupational contact, or by sharing living accommodation.

Table XII gives details of 15 primary cases of group 1 disease suspected as the source of infection for 17 secondary cases of group 1 disease.

The incubation period in Cases 2, 3, 4, 5, 6, 7, 8 (two cases), 9, 11, and 12 (one case) appears to vary from 2 to 35 weeks. Cases 1, 10, 12 (one case), 13, 14, and 15 are excluded because the evidence is incomplete.

Table XIII gives the details of seven primary group 1 cases suspected as the source of infection for seven secondary cases of group 2 disease and two secondary cases of group 1.

The incubation periods vary from 3 days to 15 weeks.

Relation Between Group 1 and Group 2

The data provided by the Wheatley "epidemic" and Tables XII and XIII pose more questions than answers in relation to infectivity and incubation period. Is there a relationship between group 1 and group 2 cases? Is it conceivable that the association of group 1 primary cases and group 1 and group 2 secondary cases can be purely coincidental?

Arbitrary separation of the cases in the Wheatley epidemic into two separate disease states permits a tentative conclusion as regards the incubation period. That the infectivity is low is the only general conclusion possible.

Table XIV shows the association in five families of five primary group 2 cases with eight secondary group 2 cases.

TABLE XIV

Case No.	Primary Group 2 Cases	Age	Contacts: No. Examined	Contacts: P.B.—Haem.+ Group 2	Days after Contact with Primary Case	Notes
1	R.M.	6	4 (family)	Z.M.; D.M.; M.M.	6; 18	Sister of R.M.; ,, ,, ,, Mother ,, ,,
2	R.S.	33	3 ,,	M.S.; P.S.	10; 9	Daughter of R.S.; Son of R.S.
3	H.R.	6	None	D.R.	2	Simultaneous infection. Siblings
4	G.S.	6	2 (family)	Mrs. S.	4	Mother of G.S.
5	E.J.	7	3 ,,	D.J.*	Uncertain	Brothers

*D.J. showed complete absence of symptoms.

The incubation period in Cases 1, 2, and 4 appeared to be between 4 and 18 days, with the probability of shared infection in Cases 1, 3, and 5. In one family four members, in another three members, were infected, and 10 of the 13 cases were in children under 8 years of age. These facts suggest that in favourable circumstances the disease has a moderately high degree of infectivity, especially in young children.

In these five family groups there was no secondary case of group 1 disease, and the infection appeared to run true.

Incidence of Glandular Fever Among the General Population

Data upon which to base an opinion concerning the incidence of the disease on the general population are meagre

and unsatisfactory because most published epidemiological studies record observations upon selected groups—Service personnel, students, nurses, or hospital admissions.

Further difficulties are that: (1) the disease is not notifiable; (2) there are important differences in the diagnostic standards employed by different laboratories; (3) no attempt is made to confirm a clinical diagnosis in a high proportion of cases; (4) a small number of patients never consult a doctor or have the disease "on their feet."

Newell (1957) analysed the reported incidence of glandular fever on the general population as revealed by the returns of cases identified by a positive Paul–Bunnell reaction from the regional laboratories. He fully recognized that such evidence indicated only the minimal incidence.

In 1955, in the Midland Region as defined by the Registrar-General, there was an incidence of 2.6 per 100,000 of population. For comparison, the population within the boundaries of Oxford City was selected because the profession had been alerted to make full use of laboratory facilities to confirm clinically suspected cases of glandular fever, and this professional co-operation in the field study was likely to be more complete than in the rural areas.

In 1955, in Oxford City, the incidence of P.B.+ cases (group 1) was 56 per 100,000, over 20 times the incidence in the Midland Region in which the city is located. The incidence of P.B.− Haem.+ cases (group 2) was 12 per 100,000, over four times the incidence of the regional incidence of P.B.+ cases. This evidence clearly indicates that there is a higher incidence of P.B.+ (group 1) disease on the general population than has hitherto been recognized.

One further point was examined. While it is certain that a few patients have the disease "on their feet," it is equally probable that this number is very small. In May, June, and July, 1957, the period of highest seasonal incidence, 231 healthy blood donors were examined as controls. Only two positive Paul–Bunnell reactions were found—one in a fully proved case of P.B.+ (group 1) disease two years previously, the other in a patient considered by the doctor to have had glandular fever four months previously but no steps being taken to confirm the clinical diagnosis.

Discussion

The term "glandular fever" has been employed throughout to indicate that in the absence of any known cause the disease state so described must be considered primarily as a clinical entity.

The term "infectious mononucleosis," although favoured and fashionable in recent medical literature, has been avoided as possibly misleading.

The Paul–Bunnell test with full absorption technique was applied to 498 patients suspected to have glandular fever on clinical grounds: 242 were cases of group 1 disease (P.B.+), 100 were cases of group 2 disease (P.B.− but Haem.+), and 156 were due to other causes.

The Paul–Bunnell test in conjunction with the white-cell count and the presence of G.F. cells in significant numbers separated the clinical material into two possibly distinct disease states, the similar and dissimilar characteristics of which can be set out conveniently in tabular form (Table XV).

G.F. cells present in comparable and significant numbers about the 14th day in each disease state are found to persist twice as long in the P.B.+ cases as in the P.B.− cases.

From the purely clinical point of view, group 1 cases have been distinguished from group 2 cases as being on the whole more severely ill and presenting some worrying clinical pictures.

The seasonal, age, and sex incidence of the two disease states present unequivocal differences which have been illustrated in the earlier part of the paper.

The infectivity of either disease is low by comparison with other infectious diseases of viral or bacterial origin.

TABLE XV

Characteristic	Glandular Fever	
	242 Cases (Group 1) P.B.+	100 Cases (Group 2) P.B.− Haem.+
Clinical symptoms and signs	Indistinguishable as regards onset, symptoms, and clinical signs	
Mortality	Nil	Nil
Morbidity: severity	Severe or moderately severe; 5% gave cause for anxiety	Moderately severe to mild; in retrospect a milder disease
Undetected cases ..	Rare; occasional	Rare; occasional
Seasonal incidence	Increase in April, May, June, July	No regular seasonal changes detected, occasional peaks
Age incidence ...	Rapid rise to 20–29 age group, followed by rapid fall	Maximal 0–9 age group, with steady fall thereafter
Sex ,, ..	Overall equal M. and F., but age-group differences	Males exceed females throughout age groups and overall 2: 1
Epidemiology, infectivity	Probable but unproved low infectivity	Low infectivity, but definitely infectious. Five family "epidemics"
Incubation ..	3 days to 35 weeks	4 to 10 days
Association: Groups 1 and 2	Occasional group 2 cases with primary group 1 cases	No group 1 cases with primary group 2 cases
Haematology ..	W.B.C. and G.F. cell count indistinguishable in active disease state; approx. 80% fully positive by 14th day, i.e., G.F. cells numerous or moderate numbers	
	6th week, 50% still show G.F. cells	5th week, 25% still show G.F. cells
	19th week, normal film	8th week, normal film

The problem of nomenclature, in the absence of a known aetiology, is very real and cannot be lightly dismissed.

If the term "infectious mononucleosis" is considered preferable to the term "glandular fever," what are to be regarded as the definitive diagnostic criteria?

In the absence of any more reliable evidence, the clinician is dependent upon the evidence provided by the Paul–Bunnell test and examination of the peripheral blood film; the technique of the former and the precision of differentiation of the latter have been established for nearly 20 years (Downey and McKinlay, 1923; Davidsohn, 1938; Barrett, 1941). The use of improved techniques upon the available clinical material has multiplied the clinical problems.

If a positive Paul–Bunnell reaction is considered essential to establish a diagnosis of glandular fever (infectious mononucleosis), it has been shown that in the present field study one in every three of clinically suspect cases is seronegative and fails to qualify.

In the past 17 years similar results have been obtained by many clinical observers, who, faced with this problem of definition and nomenclature, have found a solution in a variety of ways, three of which are considered.

Leibowitz (1956), in a fighting retreat from the position adopted by him in 1953 that a positive Paul–Bunnell test "can be utilized as an almost absolute yardstick for the diagnosis of infectious mononucleosis," now considers that "the validity of the diagnosis of infectious mononucleosis in seronegative cases still remains to be established with certainty, and will continue in some doubt until the aetiologic agent is identified and an unquestioned diagnostic test results."

Niederman (1956), reviewing cases admitted to the Yale–New Haven Medical Centre, 1946–55, found 166 "clinically acceptable" as cases of infectious mononucleosis, and considered these 72 seropositive and 94 seronegative cases as examples of the *same disease*.

Shubert *et al.* (1954), reporting upon 27 patients Paul–Bunnell negative but otherwise satisfying the clinical and haematological qualifications for a diagnosis of infectious mononucleosis, considered these cases "to be examples of a *different disease*, although closely allied to infectious mononucleosis." Disinclined to employ the term "seronegative infectious mononucleosis" because seronegativity was not the only feature differentiating this from the seropositive disease, the term "epidemic variant of infectious mononucleosis" was adopted.

These three viewpoints among many are representative of the difficulty of finding a satisfactory terminology.

The present field study supports the main contention of Shubert *et al.* that seronegative cases should be regarded as examples of a *different disease*. The characteristics which they selected as points of differentiation between seropositive and seronegative disease with their limited series of cases are not substantiated by the present study, but other characteristics appear to provide even more striking evidence. Thus, Shubert *et al.* considered that there were notable differences between the two disease states as regards the incidence of pyrexia, sore throat, and rashes, but this is not supported by the present study. Nor is the contention supported that in the seropositive disease lymphocytes exceed 50% of the total white cell count, whereas in the seronegative disease they tend to be less than 50% of the total count.

From the clinical standpoint, the really notable features have been set out in Table XV—namely, unequivocal differences in the age, sex, and seasonal incidence of the two diseases, and as regards laboratory findings the fact that the rate of disappearance of G.F. cells from the peripheral blood distinguishes the two diseases.

If the adjective "infectious" is employed, it is clear that the attribute of infectivity is a feeble characteristic of each disease state, but is more highly developed in the seronegative disease than in the seropositive.

Summary

Over a period of 30 months, 498 cases suspected on clinical grounds to be cases of glandular fever were found to comprise 242 cases Paul–Bunnell positive, 100 cases Paul–Bunnell negative and haematologically positive, and 156 cases due to other diseases.

On purely clinical grounds it has not been possible to distinguish seropositive cases from seronegative cases other than in retrospect: seropositive cases tend to be the more severe.

There were notable differences in the seasonal trends and in the age and sex incidence of the two disease states.

The infectivity of either disease state was low, but the seronegative disease appeared to be the more infectious.

Average data are presented about the duration of the positive Paul–Bunnell reaction and the associated presence of G.F. cells in the peripheral blood film.

A positive Paul–Bunnell reaction is found approximately twice as long as G.F. cells in the peripheral blood film.

A doubtful positive Paul–Bunnell reaction, too weak to titrate, has been found to be significant and associated either with an incipient phase or, more usually, a regressive phase of the seropositive disease.

In seropositive cases the G.F. cells are present in significant numbers in the peripheral blood film approximately twice as long as in seronegative cases.

We gratefully acknowledge the assistance of the members of the Glandular Fever Committee, of the hospital laboratory services, of the general practitioners, of the C.O. Military Hospital, Wheatley, and particularly of Dr. Rosemary Biggs, who collaborated in the collection of data for this field study.

REFERENCES

Barrett, A. M. (1941). *J. Hyg. (Lond.)*, **41**, 330.
Davidsohn, I. (1938). *Amer. J. clin. Path.*, **8**, Techn. Suppl., **1**, 56.
Downey, H., and McKinlay, C. A. (1923). *Arch. intern. Med.*, **32**, 82.
Leibowitz, S. (1953). *Infectious Mononucleosis*. Grune and Stratton, New York.
—— (1956). *Ann. intern. Med.*, **44**, 717.
Newell, K. W. (1957). *J. clin. Path.*, **10**, 20.
Niederman, J. C. (1956). *Yale J. Biol. Med.*, **28**, 629.
Pfeiffer, E. (1889). *Jb. Kinderheilk.*, **29**, 257.
Shubert, S., Collee, J. G., and Smith, B. J. (1954). *Brit. med. J.*, **1**, 671.

ACUTE APPENDICITIS

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The number of deaths resulting from acute appendicitis in England and Wales was remarkably constant for the years 1935 to 1938, the successive annual totals being 3,178, 3,052, 3,039, and 3,027. By 1944 the number of deaths had fallen to 1,881, and since then the steady decline in mortality has been maintained, the comparable total for 1954 being 969 (Registrar-General, 1935–8, 1944, 1954). The major factor in bringing about this fall in mortality has been the advance in the treatment of peritonitis. It is generally accepted that further reduction in the mortality will be achieved only if earlier diagnosis allows surgical intervention before the onset of complications due to the spread of infection beyond the appendix.

Recent articles on appendicitis have focused attention on treatment, and we thought that a study with emphasis on diagnosis might be of value. Few problems of diagnosis present more difficulty to the general practitioner or surgeon, and one of the main difficulties is caused by the frequency with which the onset and clinical features are atypical, especially in the very young and very old patient. As with acute pancreatitis, the greatest aid to diagnosis of appendicitis is a constant awareness of its possibility.

Material

The 549 patients who form the material for this study were admitted to one surgical charge of the Royal Infirmary of Edinburgh over a period of three years (1953–6), and in all of them the diagnosis of acute appendicitis was proved at operation. Most of the patients comprising the series were operated on by one surgeon and the remainder were under his close supervision, so that the indications for operation, the classification of the operative findings, and the operative and post-operative treatment were uniform throughout. None of the patients was treated conservatively.

Classification of Patients.—We have adopted a modified form of the simple classification used by Gilmour and Lowdon (1952), Rees (1952), and Wolff and Hindman (1952) (Table I). In our series 80% of patients were operated on

TABLE I.—*Classification*

Group	Condition	No. of Patients
1	Acute appendicitis	441 (80·3%)
2	Acute perforated appendicitis with localized peritonitis	25 (4·5%)
3	Acute perforated appendicitis with abscess formation	39 (7·1%)
4	Acute perforated appendicitis with generalized peritonitis	44 (8·1%)
	Total	549 (100%)

before the infection had spread beyond the appendix. In the remaining 20% infection had spread to such an extent that drainage of the area was necessary.

Age and Sex Incidence (Table II).—None of the patients in this series was under the age of 12 years; 64% were under 30 years of age and only 5% were 60 or more. Table III shows that with advancing age the percentage of patients with simple acute appendicitis diminishes whereas the percentage with perforated appendicitis increases. For example, the ratio of complicated to simple appendicitis was 1:8 in the second decade, 1:2 in the fifth decade, and 3:2 in patients of 60 and over.

TABLE II.—*Age Incidence*

No. of Patients	Age Group in Years						Total
	12–19	20–29	30–39	40–49	50–59	60+	
Male ..	75	73	30	25	27	13	243
Female	111	93	35	29	22	16	306

TABLE III

Age	No. of Patients	Group 1	Groups 2, 3, 4
10–19	186	164 (88%)	22 (12%)
20–29	166	148 (89%)	18 (11%)
30–39	65	52 (80%)	13 (20%)
40–49	54	38 (70%)	16 (30%)
50–59	49	28 (57%)	21 (43%)
60+	29	11 (38%)	18 (62%)

Duration of Symptoms

Comparison of the average duration of symptoms in the different age groups is misleading because in the older patient a history of relatively mild symptoms for several days or even several weeks is common. To obtain a more accurate comparison and to avoid overestimation in the older age groups, the patients in the series with vague symptoms of long duration were assessed only according to the duration of their acute symptoms. Only 451 out of the 549 patients are included in the analysis of the duration of symptoms.

Table IV shows that 31.9% of the 451 patients were admitted to hospital within 12 hours of the onset of symptoms, 63.9% within 24 hours, and 91% within 48 hours.

TABLE IV.—*Duration of Symptoms in* 451 *Cases*

		12 Hours	24 Hours	48 Hours	Over 48 Hours
All groups	All ages	144 (31·9%)	288 (63·9%)	410 (91·0%)	41 (9%)
	Under 50	132 (34·9%)	249 (65·9%)	351 (92·9%)	26 (6·9%)
	50+	12 (16·4%)	39 (53·4%)	59 (80·9%)	15 (19·1%)
Group 1	All ages	124 (36·9%)	246 (73·2%)	331 (98·5%)	5 (1·5%)
	Under 50	117 (31·0%)	220 (58·0%)	299 (99·6%)	1 (0·4%)
	50+	7 (19·4%)	26 (72·2%)	32 (88·8%)	4 (11·1%)
Groups 2, 3, 4	All ages	20 (17·4%)	42 (36·5%)	79 (68·7%)	36 (31·3%)
	Under 50	15 (19·4%)	29 (37·2%)	50 (65·4%)	27 (34·6%)
	50+	5 (13·5%)	13 (35·1%)	29 (75·7%)	9 (24·3%)

In patients of 50 and over 19% had symptoms for longer than 48 hours and only 16% for less than 12 hours, while in those under 50 years of age the comparable figures are 8% and 35%.

Although perforation of the appendix is uncommon in the first 24 hours of illness, it occurred in 14% of the patients admitted within the first 12 hours and in a similar percentage admitted in the first 24 hours.

Clinical Features (Table V)

Abdominal Pain.—All the patients in the series complained of pain, although this was not always the first symptom. The classical textbook description of central pain moving to the right side of the abdomen was given by only 39% of all patients, more commonly by those in whom the infection had spread beyond the appendix (50%). This is to be expected if it is accepted that the localizing pain is due to peritoneal irritation, but of patients with spread of infection beyond the appendix 21.3% gave a history of central abdominal pain only.

Vomiting.—This was more common in patients in whom the appendix had perforated (74%).

History of Previous Attacks.—This was more common in patients in whom the appendix was intact, suggesting that a perforation is more apt to occur in the first attack of appendicitis.

Urinary Symptoms and Diarrhoea.—Twenty per cent. of all patients complained of urinary symptoms and 16% complained of diarrhoea.

TABLE V.—*Symptomatology and Physical Signs*

Clinical Feature	Group 1 (441 Cases)	Groups 2, 3, 4 (108 Cases)
Abdominal pain:		
Classical	161 (36·5%)	54 (50·0%)
Central only	82 (18·6%)	23 (21·3%)
R.I.F. ,, ...	133 (30·0%)	25 (23·0%)
Loin	31 (7·0%)	6 (5·5%)
Vague	34 (7·7%)	—
Tenderness maximal in right lower quadrant	438 (99·3%)	108 (100·0%)
Vomiting	231 (52·4%)	80 (74·1%)
History of previous attacks	172 (39·0%)	28 (25·9%)
Urinary symptoms	85 (19·3%)	28 (25·9%)
Diarrhoea	62 (14·0%)	25 (23·1%)
Foul breath and furred tongue	284 (64·4%)	106 (98·1%)
Muscle-guarding	338 (76·6%)	102 (94·4%)
Rebound tenderness	228 (51·7%)	78 (71·6%)
Rovsing's sign	15 (3·4%)	5 (4·6%)

Foul Breath and Furred Tongue.—These very constant findings were found in 64% of the group I patients and in 98% of those in the other groups.

Muscle Resistance.—Involuntary resistance by the muscles to palpation of the right lower quadrant of the abdomen was elicited in 76% of the 441 patients comprising group 1. In all but six of the 108 patients in the other groups, muscle resistance was marked, and where there was generalized rigidity of the abdominal muscles from diffuse peritonitis the right lower quadrant could usually be identified as the site of maximum resistance.

Blumberg's Sign.—Rebound tenderness was elicited in approximately 70% of all cases: 338 out of the 441 patients in group 1 and 78 of the 108 patients in the other three groups.

Rovsing's Sign.—Pain in the right iliac fossa on deep palpation of the left iliac fosa was elicited in only 3.5% of all patients.

Temperature (Table VI).—We regarded an axillary temperature of 98.6° F. (37° C.) as being the upper limit of normal. In 70% of the patients the temperature was not raised: 78% in group 1 and only 38% in the other groups. Of the patients under 50 years of age in whom the infection was localized to the appendix, 78% showed no rise of temperature; and in those in whom the infection had spread, 33% showed no rise. However, of the patients aged 50 and over in whom the infection had spread beyond the appendix, no less than 46% presented with normal or subnormal temperatures.

TABLE VI.—*Temperature* (*Axillary*)

Age	Groups	No. of Patients	98·6° F. (37° C.) or Less	−100° F. (−37·8° C.)	>100° F. (>37·8° C.
Under 50 years	1	402	314 (78·1%)	71	17
	2, 3, 4	69	23 (33·3%)	31	15
50 and over	1	39	30 (76·9%)	8	1
	2, 3, 4	39	18 (46·2%)	11	10

Pulse Rate (Table VII).—We regarded a pulse rate of 90 a minute as being the upper limit of normal. In patients of all ages there was no increase in pulse rate in 33% of those in whom the infection had already spread beyond the appendix.

TABLE VII.—*Pulse Rate*

Age	Group	No. of Patients	90 min. or Less	91–110 min.	>110 min.
Under 50 years	1	402	266 (66·2%)	106	30
	2, 3, 4	69	22 (31·9%)	29	18
50 and over	1	39	25 (64·1%)	13	1
	2, 3, 4	39	14 (35·9%)	21	4

Treatment

The operative treatment was standardized, and the surgical approach was usually through a muscle-splitting incision in the right iliac fossa which was converted into a muscle-cutting incision if access was inadequate. In a few cases where the diagnosis was in doubt a right para-

median incision was preferred. If drainage of the peritoneal cavity was considered necessary, the drain was brought out through the iliac incision except in cases of diffuse peritonitis, in which the drain was brought out through a separate midline stab incision. If diffuse peritonitis was present, intravenous fluid therapy and gastric aspiration were instituted as soon as the patient returned from the theatre. In the patients in whom there was gross contamination of the wound at operation, anti-gas-gangrene serum and anti-tetanic serum were given in addition to parenteral administration of penicillin and sulphonamides, or penicillin and streptomycin.

Mortality

There were six deaths in the series, an overall mortality of 1.08% (Table VIII). With one exception these were

TABLE VIII.—*Deaths*

Sex	Age	Group	Days of Post-operative Survival	Necropsy Report
M	52	1	8	Disseminated sclerosis and renal infection
F	42	4	5	Suppurative broncho-pneumonia
M	56	4	10	Pulmonary embolus
M	61	4	8	Cerebral haemorrhage
M	69	4	17	Bronchopneumonia
M	79	4	6	Rheumatic heart disease and cardiac failure

patients in whom appendicitis had given rise to peritonitis. The mortality for group 1 patients was 0.23%. The five patients in group 4 who died had complicating medical conditions which contributed to the fatal outcome. No patient died from appendix abscess despite the fact that there were almost as many patients in group 3 as in group 4.

Discussion

Appendicitis must be suspected in all patients, irrespective of age, who present with abdominal pain. Acute pain in the right lower quadrant of the abdomen is an indication for urgent operation and denotes probably that the infection has already spread beyond the appendix. That right iliac fossa pain is not associated with central pain in over 25% of all patients may be explained by the threshold for intestinal pain felt in the umbilical region being higher than that for pain produced by irritation of the parietal peritoneum (Brown, 1951).

Vomiting is a characteristic feature of the obstructive type of appendicitis, and if a marked feature the probability is that the appendix has already ruptured. Looseness of the bowels is another indication that operation should not be delayed, and as a symptom it is particularly dangerous because it may be mistaken for enteritis. A dose of castor oil may not be so important in causing rupture of the appendix as in causing delay in diagnosis, with consequent rupture of the appendix (Brown, 1951). The incidence of bowel and urinary symptoms was higher in the patients in whom the infection had spread beyond the appendix.

The characteristic breath fetor and furred tongue we consider invaluable signs. If these are absent the diagnosis of appendicitis is in doubt.

Tenderness in the right lower quadrant of the abdomen, the point of maximal tenderness varying with the position of the appendix, makes the diagnosis almost certain, and operation should not be delayed. Marked muscular resistance is a late sign, and its degree is not reliably related to the pathology of the underlying appendix. It is negligible in the elderly and in the obese subject.

Mason Brown (1956) has pointed out the unreliability in children of Blumberg's sign of rebound tenderness, as the abrupt removal of the hand from the child's abdomen is in itself a cause for alarm. In adults, however, we consider this a most reliable diagnostic sign. Rovsing's sign is uncommon, and we agree with Davey (1956), who found it in 1.7% of patients, that it is of little diagnostic value.

Brown (1951) stressed the fact that temperature and pulse rate were completely unreliable in the early diagnosis of acute appendicitis, and he stated that the majority of patients who presented with a raised pulse rate had perforated appendices at operation. However, we found that increase in pulse rate was more common in simple acute appendicitis than in appendicitis with spread of infection. Thirty per cent. of our patients had an axillary temperature exceeding 98.6° F. (37° C.), and 40% had a pulse rate greater than 100 a minute. In the group of unperforated appendicitis, 78% had no rise of temperature and 66% no increase in pulse rate. In the patients in whom the infection had spread beyond the appendix, 38% had no rise of temperature and 33% no increase in pulse rate. In patients aged 50 and over we found that 70% of those with pyrexia had perforated appendices at operation. We agree with Wakeley and Childs (1950) that "absence of pyrexia has no significance but when slight pyrexia is present operation is urgent," and, we would add, particularly in the elderly patient, in whom elevation of temperature is usually associated (70%) with the complication of spread of infection beyond the appendix.

The difficulty of early diagnosis of appendicitis remains. Ascroft (1954) has shown that the error tends to be in the direction of over-diagnosis, other diseases being diagnosed as appendicitis five times as often as appendicitis is diagnosed as something else. This mistake is three times more common in females than in males. Since early diagnosis depends on the assessment of slight clinical findings, there will be unnecessary admissions to hospital and the sacrifice of many normal appendices. However, this is no error of judgment for which the doctor should be taken to task, but rather "should be regarded as an insurance premium which is paid lest some serious catastrophe arise" (Mason Brown, 1956).

The proportion of atypical cases is invariably highest in patients in whom the appendix is perforated, and "it may be that gangrene, rupture, or abscess occurs because the patient has presented atypically" (Boyce, 1954). That the disease presents atypically at the extremes of age is well known, but it is not so well recognized that it may present atypically in the middle-aged.

Appendicitis appears to be a more fulminating process in the elderly than in the young, possibly because vascular occlusion occurs more readily, thus increasing the liability to early rupture (Maes *et al.*, 1934). The higher incidence of perforated appendicitis in the older patient—47.4% of patients aged 50 and over as compared with 16.5% of those under 50—is probably attributable to the more fulminating disease and not to delay in hospitalization, although it would appear that the diagnosis tends to be delayed in the older patient (Table IV).

Perforation of the appendix had already occurred in 62% of patients aged 60 and over. This figure corresponds closely to that given by Wolff and Hindman (1952), who found perforation in 58% of patients over 60, and by Officer Brown (1934), who found perforation in 54% of patients over 50. In young children, Abel and Allen (1950) and Mason Brown (1956) estimated the incidence of complicated appendicitis to be in the region of 40%. It would appear, therefore, that the liability to perforation is greater at the extremes of age.

That it is a dangerous policy to observe a patient while one "makes up one's mind" is apparent from the fact that the appendix had already perforated in 14% of patients admitted within 12 hours of the onset of symptoms and in a similar percentage of those admitted in the first 24 hours. Delay of even a few hours is more perilous in the elderly, as is shown by the fact that, although a smaller percentage (53) of patients aged 50 and over arrived in hospital on the first day of illness, as compared with 66% of those under 50, the incidence of perforation was twice as common in the older age group (18% as against 8%). Although patients of 50 and over made up only 13.5% of the admissions on the first day of illness, they accounted for 31% of the perforations occurring within 24 hours of the onset of symptoms.

The overall mortality in this series of 1.08% is little different from the figure quoted by Gilmour and Lowdon (1952) for a comparable series of 535 patients (1.1%). All

the deaths were in patients over 40 years of age, and the Registrar-General's figures for 1954 showed that 75% of the deaths from appendicitis occurred in patients over 40. In patients in whom the infection was confined to the appendix there were no deaths attributable to the appendicitis in the series of Gilmour and Lowdon (1952) or in that of Rees (1952), and the death in our series was due to ascending renal infection complicating disseminated sclerosis. We may conclude, therefore, that, with present-day accepted treatment based on established surgical principles, the mortality from uncomplicated acute appendicitis is at the irreducible minimum for any surgical operation.

The avoidable mortality is in patients in whom the infection has spread beyond the appendix. The combined mortality rate for our groups 2, 3, and 4 was 4.6%, which is similar to the 4.5% given by Gilmour and Lowdon and by Rees. Five of the six deaths in our series occurred in group 4, giving a mortality for diffuse peritonitis from appendicitis of 11.4%. This figure corresponds to that of Gilmour and Lowdon of 11.4% and to that of Rees of 12%, and represents a great improvement over the 30–40% mortality in similar patients 30–40 years ago.

When a diagnosis of appendicitis is made the treatment of choice is early operation. In this manner only will an increasing number of patients be operated on while the infection is still limited to the appendix.

All our patients with appendix abscess were treated by early operation. Rees found the greatest mortality in this group (7–10%), and stated that this was the hard core perpetuating the high mortality in appendicitis. With modern antibiotics we believe that it is safer to drain appendix abscesses. If the appendix presents easily at operation, we believe that it should be removed; if not, a large drain is inserted and appendicectomy carried out three months later. Furthermore, the diagnosis of perforation of the appendix is notoriously inaccurate, and without operation it is impossible to be certain whether a localized mass in the right iliac fossa is an abscess or omentum wrapped round an intact appendix, and whether the disease is spreading or localizing (Boyce, 1951). Rees has called the appendix abscess "a veritable surgical wolf in sheep's clothing."

We consider that there is a real danger that antibiotics may lead to a lesser sense of urgency in diagnosis and to the abandonment of established principles in the treatment of appendicitis. Pulaski *et al.* (1948) expressed the fear that there was a tendency to institute chemotherapy and antibiotic therapy without regard to the fundamental principles of surgical management. In early uncomplicated appendicitis there is no doubt that antibiotics are no substitute for immediate appendicectomy. With regard to complicated appendicitis, Boyce (1951) stated that it is "against all reason to argue that it is safer to permit the escape of infection from a perforated viscus to continue than it is to carry out a properly planned and skilfully executed surgical procedure," and we believe that operative treatment should be carried out provided hospital facilities are available.

If sound surgical principles are followed, details of surgical technique are of little importance, except perhaps for the question of drainage of the peritoneal cavity. Shipley and Bailey (1932) advised strongly against the indiscriminate use of drainage tubes in the peritoneal cavity because they felt that their presence promoted the formation of adhesions and increased the liability to intestinal obstruction. Bancroft (1920) reported an incidence of incisional hernia of 15% after drainage, as compared with 1.9% after wound closure without drainage. However, the complications of intestinal obstruction and incisional herniae may well be the results of the initial infection and may not be due entirely to the presence of a drainage tube.

In diffuse peritonitis from appendicitis argument over the question of drainage still arises. Wakeley and Childs (1950) advocated cleansing the peritoneal cavity by suction and then draining the superficial wound only after closure of the peritoneum. We have drained the peritoneal cavity through the gridiron incision or sometimes through a separate stab incision in the midline, the drain being shortened on the third and removed on the fifth postoperative day. We have no doubt that the immediate institution of intravenous drip therapy and gastric suction in every patient with peritonitis is an invaluable procedure. This anticipates the development of paralytic ileus and prevents distension of the bowel, thus promoting the recovery of normal peristalsis.

Summary

A review is given of a series of 549 patients with appendicitis: 64% were under 30 years of age and 5% were over 60.

No patient was treated conservatively. In 80% the operation was carried out before the infection had spread beyond the appendix, but in the remaining 20% drainage of the area was necessary. It was found that the incidence of complicated appendicitis increased in the elderly patient, and that this was not solely due to delay in diagnosis but also the more fulminating process in the elderly.

The classical textbook description of appendicitis was not often met with, and the frequency of atypical presentation is stressed. Emphasis is made on the importance of suspecting appendicitis in all patients who present with abdominal pain irrespective of age.

The characteristic breath fetor and furred tongue are important signs, and if associated with much vomiting or diarrhoea suggest that the infection has already spread beyond the appendix.

Local tenderness over the inflamed appendix, usually in the right quadrant of the abdomen, is the most important sign; it may even be the only sign, but, on the other hand, it may be absent in the very obese or elderly patient.

No reliance should be placed on the pulse rate or temperature for the early diagnosis of appendicitis. If there is a rise of temperature in the elderly patient, the infection has almost certainly spread beyond the appendix.

If operation is carried out while the infection is confined to the appendix the mortality is at the irreducible minimum for any surgical procedure. In cases in which appendicitis has progressed to abscess formation, we believe it is safer to operate and to drain the abscess. If the appendix presents, it is removed, but if appendicectomy is difficult and would require some dissection the abscess is drained.

It is emphasized that early diagnosis and prompt surgical treatment are still the most important principles in dealing with this, the most common surgical emergency.

We are indebted to Mr. W. A. D. Adamson, surgeon-in-charge, the Royal Infirmary, Edinburgh, for allowing us to treat these patients and for his help with this paper.

REFERENCES

Abel, W. G., and Allen, P. D. (1950). *Ann. Surg.*, **132**, 1093.
Ascroft, P. B. (1954). *Arch. Middx Hosp.*, **4**, 182.
Bancroft, F. W. (1920). *J. Amer. med. Ass.*, **75**, 1635.
Boyce, F. F. (1951). *Ann. Surg.*, **133**, 428.
—— (1954). *Ann. Intern. Med.*, **40**, 669.
Brown, C. J. Officer (1934). *Med. J. Aust.*, **2**, 407.
Brown, F. R. (1951). *Brit. med. J.*, **1**, 136.
Brown, J. J. Mason (1956). *J. roy. Coll. Surg. Edinb.*, **1**, 268.
Davey, W. W. (1956). *Brit. med. J.*, **2**, 28.
Gilmour, I. E. W., and Lowdon, A. G. R. (1952). *Edinb. med. J.*, **59**, 361.
Maes, U., Boyce, F. F., and McFetridge, E. M. (1934). *Surg. Gynec. Obstet.*, **58**, 32.
Pulaski, E. J., Spicer, F. W., and Johnson, M. J. (1948). *Ann. Surg.*, **128**, 46.
Rees, W. S. (1952). *Lancet*, **2**, 1199.
Registrar-General (1935-8, 1944, 1954). *Statistical Review of England and Wales.*
Shipley, A. M., and Bailey, H. A. (1932). *Ann. Surg.*, **96**, 537.
Wakeley, C., and Childs, P. (1950). *Brit. med. J.*, **2**, 1347.
Wolff, W. I., and Hindman, R. (1952). *Surg. Gynec. Obstet.*, **94**, 239.

EFFECT OF VALYL-OXYTOCIN ON THE HUMAN SUBJECT

BY

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Following their recent methods for the synthesis of oxytocin ("syntocinon"), Boissonnas *et al.* (1956) published an account of their synthesis and the biological properties of some analogues of oxytocin in which one amino-acid residue had been replaced by another. In a subsequent publication Berde *et al.* (1957) dealt in detail with the pharmacological properties of four of these compounds. They were interesting because when assayed against the international pituitary (posterior lobe) standard powder their relative activity varied according to the method of assay chosen.

In three of the analogues the isoleucyl group of oxytocin was replaced by a phenylalanyl, leucyl, or valyl residue, the compounds being designated P-, L-, or V-analogue respectively. In the fourth, named the G-analogue, the asparaginyl group was replaced by a glutamyl residue. The results of the biological asssay of synthetic oxytocin and its four synthetic analogues are summarized in the accompanying Table.

The differences in the results were surprising, especially as synthetic oxytocin, made by the method of Boissonnas *et al.* (1955), and the natural mammalian pituitary preparation ("pitocin") had given identical assays in all species tested and in *in-vitro* experiments, and had also proved indistinguishable in the human (Bainbridge *et al.*, 1956).

It therefore seemed desirable to compare one of the above-mentioned analogues with oxytocin in its effects on the human subject, and thereby to see which of the biological assays was the better representative of potency in the human. It seemed possible that these results might confirm or disprove the suitability of present pharmacopoeial methods for the assay of oxytocin or its analogues.

Valyl-oxytocin was chosen for the human tests—that is, the V-analogue—and the findings form the subject of this article.

Comparisons between synthetic oxytocin (syntocinon) and valyl-oxytocin have been made as described below; one unit of either drug being a unit according to the *B.P.* method of assay against the international standard pituitary powder.

Intrauterine-pressure Changes

Therapeutic Abortion.—Intrauterine-pressure changes were recorded in a case of therapeutic abortion at 19 weeks' gestation. No anaesthetic was given, and the injections were made intravenously. A three-point matching assay showed 0.25 unit of syntocinon to be slightly stronger than 0.05 unit of valyl-oxytocin (Fig. 1).

Patients With Dead Foetus.—Intrauterine-pressure changes were recorded on two patients with a dead foetus at approximately 28 weeks' gestation. By giving intramuscular injections at two-hourly intervals it was shown that, for the same initial rise of tone and to maintain rhythmical contractions for about two hours, the first patient required three units of syntocinon or 0.8 unit of valyl-oxytocin. In the second patient 2 units of syntocinon produced a greater rise of tone than 0.25 unit of valyl-oxytocin and less than that produced by 0.75 unit of valyl-oxytocin. The contractile rhythms produced by valyl-oxytocin persisted longer and were more regular than those produced by syntocinon, an observation also to be seen in Fig. 1. The results for the second patient are reproduced in Fig. 2.

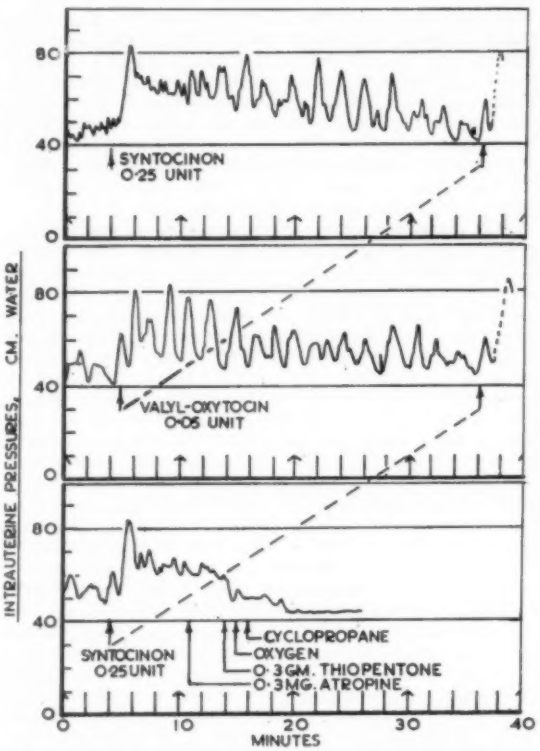

FIG. 1.—Three-point matching assay of intravenous syntocinon and valyl-oxytocin in an unanaesthetized patient sedated with "omnopon" 10 mg., scopolamine 0.3 mg., and chlorpromazine 12.5 mg.; intramuscular injection 30 minutes before start of assay. Prior to therapeutic abortion at 19 weeks' gestation. Pressures from 2-ml. uterine balloon.

Activity of 1 ml. of Solutions of the Cyclic Octapeptides in Units of International Standard Pituitary (Posterior Lobe) Powder in Different Tests (from Berde et al., 1957)

	Isolated Rat Uterus	Chicken Blood Pressure	Milk-ejection Pressure (Rabbit Mammary Gland)	Cat Uterus *in situ*	Antidiuretic Activity (Non-anaesthyetized Rats)	Pressor Activity (Spinal Cats)
Synthetic oxytocin	8·0 (±0·22)	8·1 (±0·16)	8·3 (±0·23)	10·7 (±0·9)	0·09 (±0·05)	0·07
P-analogue	2·7 (±0·11)	2·2 (±0·08)	5·8 (±0·37)	2·4 (±0·3)	2·8 (±1·2)	0·5
L-analogue	0·25 (±0·01)	0·33 (±0·01)	2·2 (±0·44)	2·3 (±0·4)	0·15 (±0·08)	0·15
V-analogue (valyl-oxytocin)	2·8 (±0·11)	3·2 (±0·08)	15·0 (±0·75)	16·7 (±1·3)	0·04 (±0·02)	0·015
G-analogue	<0·0025	<0·02	0·025 (±0·003)	0 (Up to 1 ml. kg. i.v.)	0 (Up to 1 ml. 100 g. s.c.)	0 (Up to 0·5 ml. kg. i.v.)

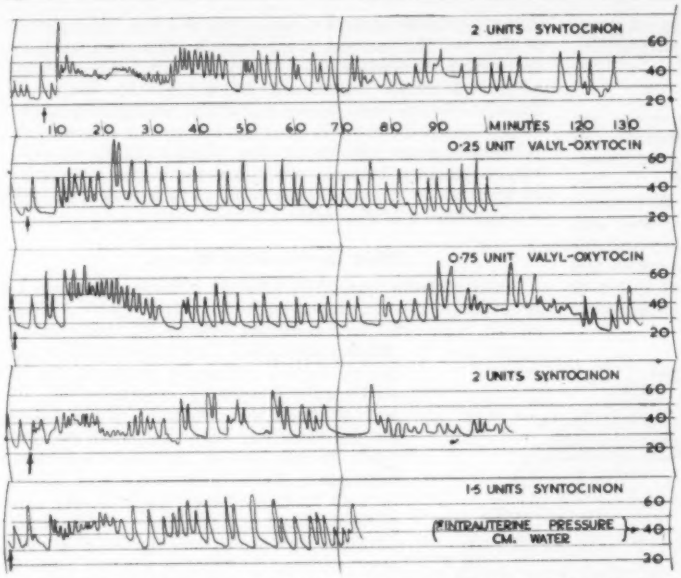

FIG. 2.—Intrauterine pressure produced by intramuscular injections of syntocinon and valyl-oxytocin compared. 28 weeks' gestation; dead foetus.

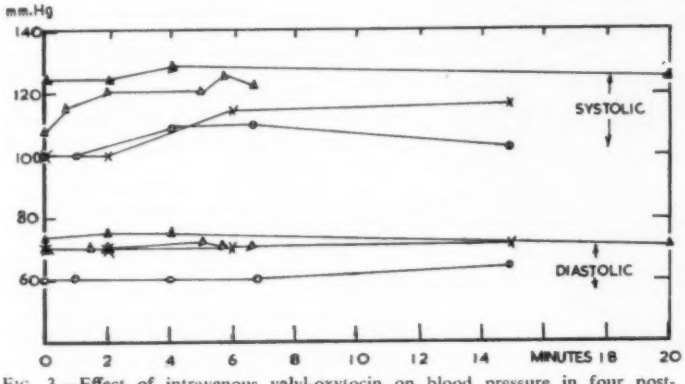

FIG. 3.—Effect of intravenous valyl-oxytocin on blood pressure in four post-partum patients. Doses: O and X, 0.5 unit; △ and ▲, 0.25 unit.

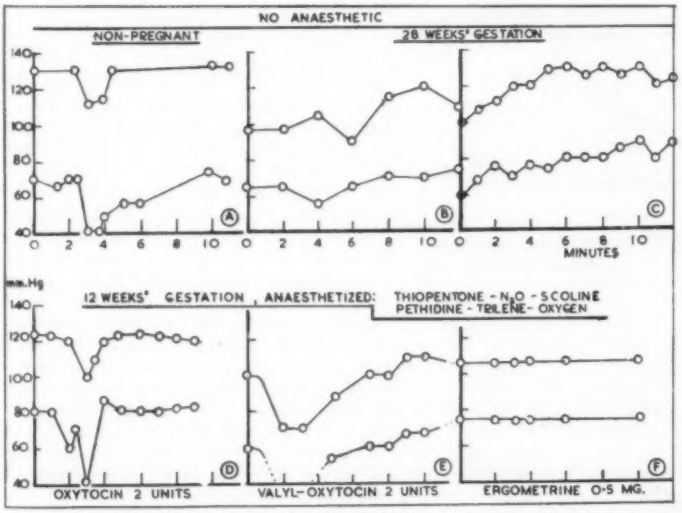

FIG. 4.—Oxytocics, intravenous injections, and blood pressure. Curves A–F are explained in the text.

Blood-pressure Changes

The blood pressure was recorded during the courses of the intramuscular injections given in Section 2, above. Large intramuscular doses of syntocinon, 2 or 3 units, caused a gradual diminution in blood pressure from values of 100/70 to 70/60 mm. Hg, whereas equiactive oxytocic doses of valyl-oxytocin, 0.5 to 0.8 unit, resulted in a slight rise in blood pressure to 115/75 mm. Hg. These findings led to the making of more exact comparisons with intravenous doses, the results of which are reproduced in Figs. 3 and 4.

Fig. 3 shows the result of giving 0.25 and 0.5 unit of valyl-oxytocin intravenously to four patients on the third post-partum day. The blood pressure was taken every minute for five minutes, then every five minutes for 15 minutes. No fall in pressure was demonstrated, and in three patients there was a rise in systolic pressure. These injections induced uncomfortable uterine contractions lasting throughout the test, and the associated uterine ischaemia may well account for the slight pressure rise. Fig. 4 demonstrates that a sudden drop in blood pressure can be provoked by larger doses of valyl-oxytocin. In this respect valyl-oxytocin resembles oxytocin, and the test appears to parallel the pharmacopoeial assays, since about 2 units of either drug is required to produce this effect.

Curve A of Fig. 4 is reproduced from Mayes and Shearman (1956) and curve D from Schild *et al.* (1951). The other four curves were made at the present time. Curves B and C were on the same patient on successive days, while curves E and F were made sequentially on another patient prior to evacuation of the uterus. Where the pregnancy is advanced and there is a large uterine blood supply the fall in blood pressure tends to be masked by the rise brought about by the simultaneous uterine contraction, but a distinct kink is noticeable in curve B. These curves are particular examples, and doubtless many differences would be found between these and patients

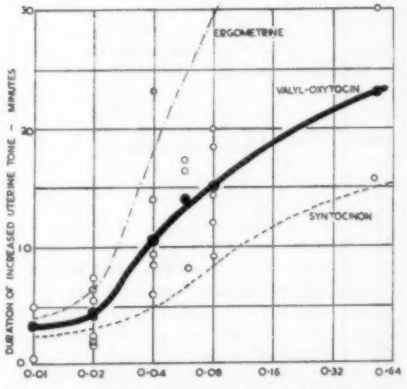

FIG. 5.—Uterine tone produced by intravenous injections of valyl-oxytocin in post-partum patients compared with those of syntocinon and ergometrine. ●=Averages. O=Observations with valyl-oxytocin. Dose: Syntocinon and valyl-oxytocin in units; ergometrine in mg.

with abnormally raised blood pressure, toxaemia of pregnancy, and in different stages of gestation or the puerperium.

Changes in Uterine Activity

Valyl-oxytocin was given to 30 patients on the second and the third post-partum day with simultaneous recording of uterine activity by means of an abdominal tocodynamometer. The drug was given intravenously after a baseline of uterine activity had been recorded for about 20 minutes. The change in uterine activity recorded in this way with oxytocin injections shows a response which is very variable in height, a factor dependent on the uterine contents and whether the uterus hardens round the blood clot within or expels it. The duration of raised uterine tone, however, shows a graded relation to dose, and this has been plotted in Fig. 5. The method is the same as that used to assay syntocinon (Bainbridge *et al.*, 1956). In Fig. 5 the curve for syntocinon is also reproduced, and a curve has been constructed from an ergometrine assay (Myerscough and Schild, 1955). Valyl-oxytocin is seen to occupy an intermediate position between these two curves. Depending on the dose, valyl-oxytocin is between two and five times as long-acting as oxytocin in raising uterine tone. Three typical records are reproduced in Fig. 6.

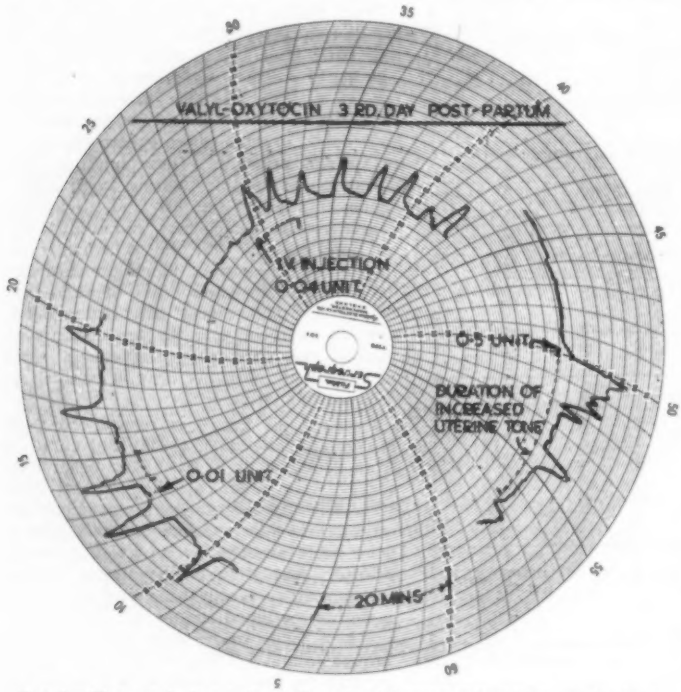

FIG. 6.—Three typical records of effect of valyl-oxytocin in raising uterine tone.

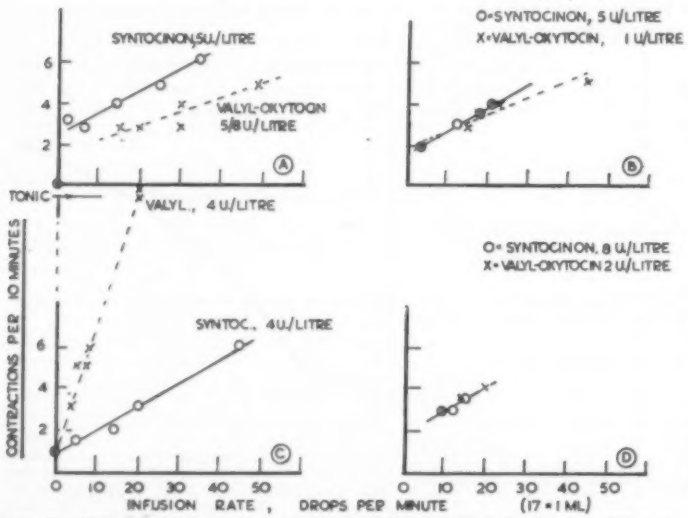

FIG. 7.—Records of intravenous injections of valyl-oxytocin, in 5% dextrose, in four intra-partum patients at term. Curves A–D are explained in the text.

Effect on Parturient Women

Valyl-oxytocin was given to eight parturient patients by intravenous infusion employing concentrations varying from 0.5 to 4 units per litre of 5% dextrose. It behaves similarly to oxytocin, readily producing a good contractile rhythm if the infusion rate is suitably adjusted. No abnormal effects were noticed, and the babies did not show any signs that could be attributed to intrauterine anoxia or abnormal pressures. A matching assay was carried through on four of these patients who were given synthetic oxytocin and valyl-oxytocin infusions alternately, and the infusion rates were adjusted to provide various rates of contraction; at least four changes were made on each patient. The first result of the infusion is to start a contractile rhythm, if one is not already present. Increasing the infusion rate increases the rate of contractions, and, eventually, further increases in rate cause the tone between contractions to rise. A rise in tone is not considered desirable, since it may lead to foetal anoxia, and the assay is not intentionally pursued to such concentrations.

The results of the four assays are reproduced in Fig. 7. In equal concentrations valyl-oxytocin was considerably more potent than oxytocin (curve C). Diluted eight times (curve A), valyl-oxytocin was noticeably less potent. Diluted 5 times (curve B, valyl-oxytocin was slightly less potent, and at four-times dilution there was no perceptible difference (curve D). Not only do these four assays point to the same conclusion, but they are consistent numerically between themselves to an accuracy of + or − 10%.

Discussion

The assay shows that, as an excitor of contractions, valyl-oxytocin is four times as potent as synthetic oxytocin in the human subject even though the two substances are equiactive when assayed by the pharmacopoeial method—that is, by depression of the blood pressure in a chicken and the rat uterus method.

If, however, valyl-oxytocin is diluted four times so as to be equiactive with oxytocin in the human subject, then it is also practically equiactive in terms of the rise in milk ejection pressure in the rabbit mammary gland and in its action on the cat uterus *in situ*. Synthetic and natural oxytocin give roughly identical results when tested by any of the above methods, and therefore it appears that the milk-pressure assay, or that of cat uterus *in situ*, might with advantage be used in addition to the pharmacopoeial methods.

Doses of valyl-oxytocin which are equiactive in the human subject with oxytocin

in exciting uterine contractions are not equiactive in their effects on blood pressure. Blood pressure is affected only by extremely large doses of oxytocin, 2 units intravenously usually being required to produce a pressure fall lasting about a minute and occurring two to three minutes from the time of injection. Half a unit of valyl-oxytocin does not produce this effect, but 2 units will do so. In this respect the *B.P.* assay of the two substances on chicken blood pressure or isolated rat uterus is parallel to the comparison in the human subject so far as the limited tests we have made are able to show.

Summary

Following their synthesis of oxytocin, Boissonnas *et al.* (1956) prepared analogues of oxytocin having actions which were similar qualitatively but which differed quantitatively.

A comparison has been made of the actions of one of these analogues, valyl-oxytocin, with those of synthetic oxytocin in animals and in man.

The results are discussed, with special reference to the present methods of assay.

The oxytocin and valyl-oxytocin used in this work were generously supplied by Messrs. Sandoz, Basle, Switzerland. Dr. H. Holgate, of Sandoz, London, has kindly supplied us with the published information on the analogues of oxytocin. The preparations of oxytocin and valyl-oxytocin have been standardized by the Sandoz Laboratories, Basle, against the International Standard Pituitary Powder. Our thanks are due to the editor and publishers of the *British Journal of Pharmacology and Chemotherapy* for permission to reproduce the Table, and to the editor of the *Lancet* and of the *Journal of Obstetrics and Gynaecology of the British Empire* for permission to reproduce Figs. 4a and 4d.

In the post-partum assays I was grateful for the assistance of Miss M. N. Bainbridge and also of Miss J. Farrow, who assisted with the intravenous infusion assays. The staff of the Obstetric Unit, and in particular the Director, Professor W. C. W. Nixon, encouraged and assisted the work in many respects. Dr. H. O. Schild, reader in pharmacology, University College, London, has given generous assistance in planning the work.

REFERENCES

Bainbridge, M. N., Nixon, W. C. W., Schild, H. O., and Smyth, C. N. (1956). *Brit. med. J.*, **1**, 1133.

Berde, B., Doepfner, W., and Konzett, H. (1957). *Brit. J. Pharmacol.*, **12**, 209.

Boissonnas, R. A., Guttmann, St., Jaquenoud, P. A., and Waller, J. P. (1955). *Helv. chim. Acta*, **38**, 1491.

—— —— —— Konzett, H., and Berde, B. (1956). *Nature (Lond.)*, **178**, 269.

Mayes, B. T., and Shearman, R. P. (1956). *J. Obstet. Gynaec. Brit. Emp.*, **63**, 812.

Myerscough, P. R., and Schild, H. O. (1955). *Proc. roy. Soc. Med.*, **48**, 679.

Schild, H. O., Fitzpatrick, R. J., and Nixon, W. C. W. (1951). *Lancet*, **1**, 250.

"Recent work on the hormonal prevention of conception in man by Pincus and his colleagues has depended on the suppression of ovulation and has been made practicable by the preparation of orally-active substances with progesterone-like activity. One of these seems to be promising in Pincus's clinical experiments. Presumably it overwhelms the follicular phase of the cycle partly by local inhibition and partly by interference with pituitary activity. It seems, however, that treatment is necessary over some 20 days in each cycle, probably in order to ensure that ovulation is prevented and not merely postponed, and for this and other reasons this work cannot yet be said to have put oral contraception on a practical basis. But it is most promising and exciting." This is from an article by Dr. A. S. PARKES, F.R.S., "Towards Oral Contraception," which describes the origin and work of the Oliver Bird Trust and the Council for the Investigation of Fertility Control (*Family Planning*, 1958, **7**, 9). *Family Planning* is published quarterly and is obtainable by non-members from the Family Planning Association, 64, Sloane Street, London, S.W.1, price 2s. 6d. (post free) annually.

PROLONGED REMISSION IN CHRONIC LYMPHATIC LEUKAEMIA

BY

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The duration of life of patients with chronic lymphatic leukaemia has been variously quoted, but Tivey (1954), in an analysis of 46 series of cases reported in the literature between 1925 and 1951, estimated the median survival to be about 1.6 years after commencement of therapy and 2.6 years after the onset of the first clinical symptoms. He found, however, that the survival curves were "badly skewed," and it is generally agreed that individual patients can live for a very much longer time. Amongst the longest survivors with chronic lymphatic leukaemia recorded is one of 29 years (Marlow and Bartlett, 1953) and one of 25 years (McGavran, 1938).

A number of cures of leukaemia have been reported in the literature. According to Forkner (1938) and Wintrobe (1956), in only a few can the possibility of a cure be considered. Schott (1955) describes the case of a patient with chronic lymphatic leukaemia who was symptom-free and had a normal peripheral blood count 10 years after radiation treatment.

The following case is presented as a further example of long-term remission in a patient suffering from chronic lymphatic leukaemia who is clinically well and has a normal peripheral blood count eight years after the last treatment. Marrow punctures have been carried out at various intervals during the time of observation, and are discussed below. An interesting additional feature is the development in this patient of carcinoma of the cervix, treated apparently successfully three years ago.

Case History

A married woman, then aged 49, was admitted to another hospital on February 23, 1946, with 2 weeks' history of weakness and giddiness, and 1 week's continuous vaginal bleeding following six months' amenorrhoea. There was no previous significant illness. She had had nine normal confinements. On examination at that time pallor was marked, there was a moderate generalized lymphadenopathy, and the liver and spleen were palpable. Pelvic examination did not reveal any local cause for her vaginal bleeding.

Investigations.—R.B.C., 770,000/c.mm.; haemoglobin, 2.5 g./100 ml.; W.B.C., 27,000/c.mm. (polymorphs 4%, eosinophils 1%, lymphocytes 93%, monocytes 2%). There were no nucleated red cells. Platelets, 31,000/c.mm. Bleeding-time, 10 minutes. Clotting-time, 8 minutes.

Puncture of the sternal marrow confirmed the diagnosis of lymphatic leukaemia. She was given repeated transfusions, and from March 4 to 28 was treated with urethane. This was followed by a profound fall in the W.B.C. and a tendency to spontaneous bleeding from the gums, with infection of the mouth and throat. Further transfusions, penicillin, "anahaemin" injections, and ferrous sulphate were given, with slow recovery (Fig. 1). She was discharged from hospital on August 3. Her attendance thereafter for follow-up was erratic.

On May 7, 1948, she was readmitted with a history of hot sweats, headaches, and cough. The blood count on admission was R.B.C. 1,600,000/c.mm.; haemoglobin, 5.3 g./100 ml.; W.B.C., 5,200/c.mm. (polymorphs 18%, lymphocytes 82%). Generalized enlargement of lymph nodes was again present. The liver and spleen were enlarged three fingerbreadths. Following transfusion she was transferred to Hammersmith Hospital on June 24. On admission she was very pale, and had spontaneous bruises and petechiae on both legs. Numerous large lymph nodes were found in the neck, axillae, and groins, and the liver and spleen were enlarged 6 cm. beneath the costal margin. An *x*-ray examination of the chest was normal. On June 25 a blood count showed: haemoglobin, 4.4 g./100 ml.; W.B.C., 5,500/c.mm., with 92% lymphocytes. A further sternal marrow aspiration showed the presence of numerous lymphocytes with very few cells of the myeloid and erythroid series. Approximately 90% of the lymphocytes were mature, intermediate in size, and of uniform pattern. There was a small percentage of prolymphocytes, and only 3% blasts. In the light of these findings aleukaemic lymphatic leukaemia was diagnosed. *X*-ray treatment through an anterior trunk bath was given from July 2 to 14, when it was discontinued owing to a severe fall in the leucocyte count. This finally reached 330/c.mm. In spite of the blood picture the patient's general condition remained fair. After further transfusion she was discharged on August 16 (Fig. 2A).

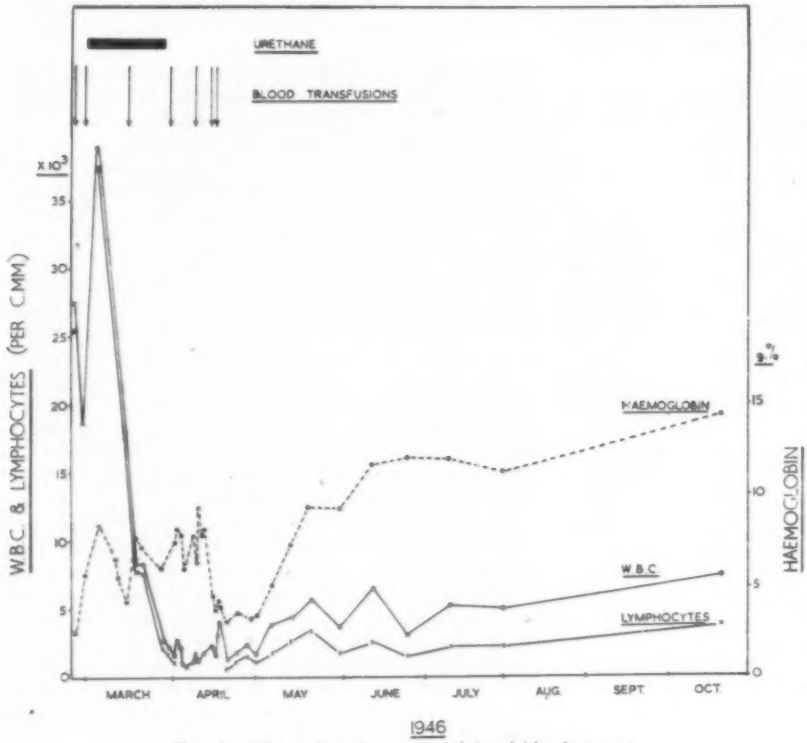

FIG. 1.—Effect of urethane on peripheral blood counts.

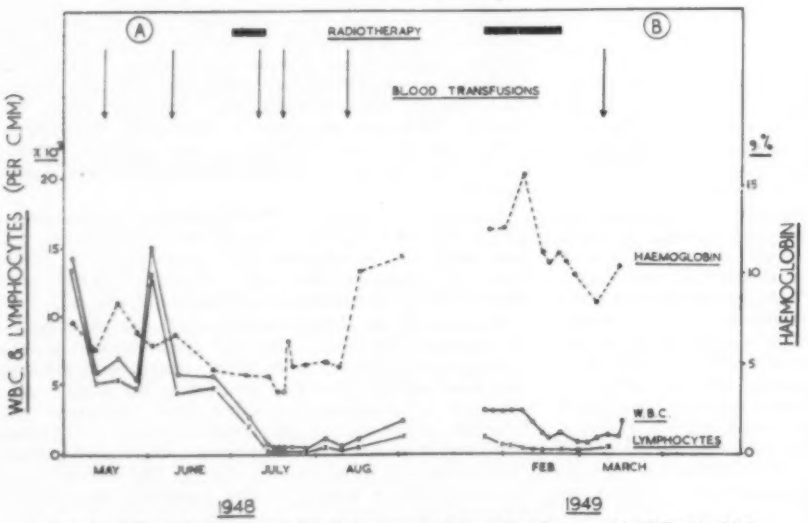

FIG. 2.—Effect of whole-trunk irradiation on peripheral blood count. (A) 1948; (B) 1949.

In January, 1949, as her lymph nodes again enlarged and she complained of lassitude, a further course of irradiation was given. Again leucopenia developed, the leucocytes falling to 800 and lymphocytes to 120/c.mm., but the general condition remained good. A transfusion was given, and she was discharged on March 18, 1949 (Fig. 2B).

By May 25 the haemoglobin had risen to 15 g./100 ml., W.B.C. 3,600/c.mm. (polymorphs 50%, lymphocytes 40%, monocytes 9%). Since that time there has been no clinical sign of relapse of the leukaemia.

In 1954 the patient developed vaginal bleeding and was readmitted on May 9. Her general condition was good. No enlarged glands were found and the liver and spleen were not palpable. Vaginal examination revealed a papilliferous tumour of the cervix spreading to the vaginal vault. The clinical diagnosis was carcinoma of cervix stage II. The blood count on admission showed: haemoglobin, 12.3 g./100 ml.; W.B.C., 6,000/c.mm. (polymorphs 80%, lymphocytes 14%, eosinophils 3%, mononuclears 3%). A sternal marrow puncture showed little evidence of the earlier lymphocyte infiltration, for the lymphocytes, mature and small, constituted 25% of the nucleated cells. The myeloid: erythroid ratio was 4:1, and both these series showed normal maturation. The picture was considered to be consistent with chronic lymphatic leukaemia in a state of remission.

Treatment was given by three intrauterine applications of radium. *X*-ray therapy to the parametria was begun, but was abandoned as the leucocytes fell to 2,000/c.mm.

She was discharged on June 19. She has remained free from clinical evidence of recurrence of either disease. Blood counts have been performed regularly, and are shown in Fig. 3. These show a normal haemoglobin, with a slight leucopenia but a normal differential count. A further bone-marrow aspiration on November 23, 1956, showed a deterioration when compared with the previous marrow of 1954. Approximately 70% of the nucleated cells were lymphocytes. These were mature, but large in size, and there was an increase in the numbers of earlier cells—12% prolymphocytes and 8% blasts. The blasts showed coarse nuclear chromatin, and basophilic agranular cytoplasm; some of these cells resembled reticulum cells, and the earlier uniformity has been lost. The peripheral blood of this same period, and subsequently, showed a normal cell distribution, with normal morphology, the lymphocytes being small mature cells.

Discussion

This case presents a number of interesting features. There can be no reasonable doubt about the correctness of the diagnosis. Clinically and haematologically the patient presented features characteristic of chronic lymphatic leukaemia. As recently as November, 1956, a marrow puncture showed findings consistent with those found in this disease, but, since the patient's second course of radiotherapy by an anterior trunk bath in early 1949, her peripheral blood picture has shown a normal haemoglobin and differential white-cell count. With regard to the latter finding, this case differs from the two longest survivors described by McGavran (1938) and Marlow and Bartlett (1953), as mentioned above, in both of whom the differential count remained abnormal throughout life. It is, however, similar to the case described by Schott (1955). Our patient is now well, with a normal peripheral count, and has had no clinical signs of the disease for more than eight years. She might therefore have been regarded as having been clinically cured.

It may be argued that this freedom from disease has been prolonged by the irradiation treatment to the pelvis given for carcinoma of the cervix in 1952. There is, however, nothing to indicate that this is in fact so. Just before this treatment the patient's total leucocyte count was 6,000/c.mm. with a normal differential count, and, following a transitory fall towards the end of the *x*-ray treatment, the leucocyte total returned to the pretreatment level. There were no symptoms or signs indicating any evidence of recrudescence or activity of the disease.

It is interesting to speculate whether the severe falls in the white-cell count which occurred during both treatments (330/c.mm. in 1948 and 800/c.mm. in 1949) were not an important factor in producing the prolonged remission. It is known from the treatment of acute leukaemia by chemotherapy—for example, 6-mercaptopurine and the folic acid antagonists—that satisfactory remissions are occasionally achieved when the marrow is almost completely destroyed by the drug and the peripheral white-cell count falls to a marked and often alarming extent. By analogy, therefore, it is possible that the *x*-ray treatment in this patient caused considerable aplasia of marrow, and that the regeneration, when it took place, was more pronounced in the erythropoietic and myeloid elements.

When considering the prognosis in chronic lymphatic leukaemia certain findings are thought to be of grave significance. Among these are marked weight loss, anaemia, marked splenomegaly, and thrombocytopenia. This patient had at least two of these—namely, a severe anaemia on presentation at the hospital and during the following three years, and a pronounced thrombocytopenia (31,000/c.mm. in February, 1946). The progress of the disease, however, in this case shows once again how difficult it is to give a definite prognosis in an individual case of chronic leukaemia.

The association of chronic lymphatic leukaemia with other forms of malignant disease has been noted by many authors—for example, Bichel (1949) and Beresford (1952). There appears, however, to be no clear causal relationship. There is also no evidence to suggest that there is any definite mutual influence on the progress of either condition, though some have suggested that there may be an inhibitory effect of the malignant disease on the leukaemia. Our patient does not throw any further light on this latter problem, and the occurrence of carcinoma of the cervix appeared to be unrelated to the presence of the leukaemia.

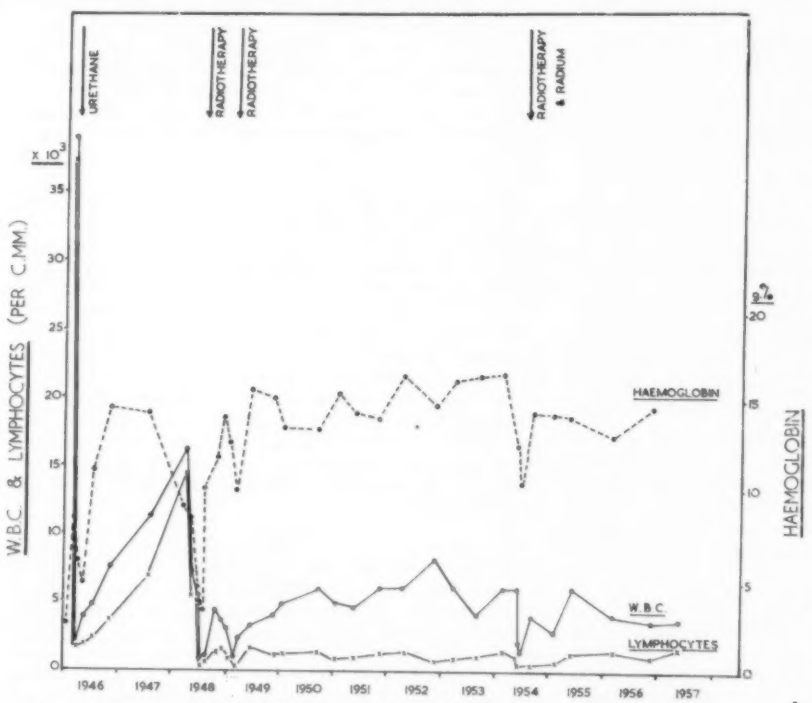

FIG. 3.—Peripheral blood counts from time of diagnosis to present time.

The most interesting feature in this case is undoubtedly the lack of correlation between the bone-marrow aspiration and the peripheral blood count findings. Although the patient appears to have been "cured" for eight years, the bone-marrow findings show a picture of chronic lymphatic leukaemia. It is obvious that the disease has been arrested and not eradicated. In the absence of normal marrow reports it is probable that a similar state of affairs may have existed in most of the reported cases of cure. It also confirms the known fact that lymphatic leukaemia can at times be a very "benign" disease.

Summary

The history and clinical findings of a patient with chronic lymphatic leukaemia first diagnosed in 1946 are described. In 1954 she developed carcinoma of the cervix, and the asso-

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ciation of leukaemia with other forms of malignant disease is briefly discussed. She has remained free of symptoms and signs of her leukaemia for eight and a half years. In spite of a normal peripheral blood count, marrow aspiration reveals findings consistent with chronic lymphatic leukaemia. This lack of correlation as well as certain features affecting the prognosis in this disease is discussed.

We thank Professor J. V. Dacie for advice; and Dr. C. D. Coyle, medical superintendent, Whittington Hospital, for his help in making available to us the early case notes on this patient.
We should also like to acknowledge the help of Miss J. M. Gartside in preparing the graphs.

REFERENCES

Beresford, O. D. (1952). *Brit. J. Cancer*, **6**, 339.
Bichel, J. (1949). *Blood*, **4**, 759.
Forkner, C. E. (1938). *Leukemia and Allied Disorders*, p. 198. Macmillan, New York.
McGavran, C. W. (1938). *Ann. intern. Med.*, **12**, 396.
Marlow, A. A., and Bartlett, G. R. (1953). *J. Amer. med. Ass.*, **152**, 1033.
Schott, M. (1955). *Brit. med. J.*, **1**, 877.
Tivey, H. (1954). *Amer. J. Roentgenol.*, **72**, 68.
Wintrobe, M. M. (1956). *Clinical Hematology*, 4th ed., p. 960. Kimpton, London.

CURRENT SMOKING HABITS IN 1957

BASED ON MASS RADIOGRAPHY SURVEYS IN THE MIDLANDS

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In conjunction with our colleagues of the mass radiography service in the Birmingham region, we are engaged in carrying out an investigation of certain aspects of cases of bronchial carcinoma discovered by mass radiography. Naturally we must examine the smoking habits of the patients concerned in relation to those of a control group. In considering this aspect of the inquiry we encountered the absence of reliable data relating to the smoking habits of the population in this region. The only exceptions are the data given by Lowe (1956) for tuberculous patients and for a control group chosen from in-patients and out-patients of "acute" hospitals in Birmingham. The "catchment area" of these hospitals and clinics is, however, considerably smaller than the area being examined by our units, and we therefore decided to use some of our routine mass radiography surveys to obtain data about current and past smoking habits of the population in the Midlands. In this way we hoped to obtain standards against which to compare our findings in the investigation of bronchial carcinoma.

The main purpose of this paper is a comparison of our groups *inter se*, and for this an analysis of "current smoking habits" in contradistinction to "total smoking habits" seemed to be sufficient. An analysis of "total smoking habits" has been reserved for a future study, in which we shall attempt to compare our findings with the data by other authors, who mostly use this definition.

We consider it important to stress that the investigation took place during the first five months of 1957, and that the collection of data was completed before the issue of the Medical Research Council's report (1957) and before the subsequent statement about smoking risks by the Parliamentary Secretary to the Minister of Health on June 27, 1957. Furthermore, during the period of collecting data there was no marked change in the price of cigarettes or tobacco. We hope to re-investigate the same groups in the future, with a view to possible changes in smoking habits brought about by the changing economic or psychological climate of the country.

Definition of Smoking Habits.—In this paper a "current smoker" is defined as a person *who at the time of the interview* smoked as much as one cigarette a day or ½ oz. (14 g.) of pipe tobacco a week. Mixed smokers have been classified according to prevalent habit. The very small number of cigar smokers has been disregarded.

Methods of Investigation

It was decided to carry out the investigation during mass radiography surveys held in two industrial areas (Birmingham and Stoke-on-Trent), in a small town in Herefordshire (Leominster), in Shropshire, and in the urban district of Stourbridge (Worcestershire). These areas are typical of the places where mass radiography surveys are held in the Midlands. The surveys were not planned primarily with a view to obtaining a record of smoking habits, but were part of the normal mass radiography programme of each unit in accordance with the policy and procedure in this region. In fact, it was decided to record this information only shortly before the surveys began.

The groups examined were: (1) 7,680 employees of a large electrical engineering company in Birmingham; (2) 2,774 underground and surface workers in three North Staffordshire coal-mines; (3) 2,452 workers in ten pottery factories in Stoke-on-Trent, manufacturing general earthenware, glazed tiles, and sanitary earthenware; (4) 6,571 persons attending open public sessions in Herefordshire, in Stourbridge (Worcestershire), and in Shropshire. This last group included housewives, office workers, shop people, young persons, and other volunteers from the general public. The large majority of these persons were not employed in industry.

The proportion of employees examined was about usual for mass radiography industrial surveys in this region: 70% of the employees of the Birmingham factory responded, 69% of the pottery workers, and 73% of the colliery workers in the Stoke area. In the Herefordshire survey 63% of the available population attended (Posner, 1958).

The clerks of the units carrying out the surveys were thoroughly briefed to ask a standard set of questions relating to current and past smoking habits, and to enter the answer by simple coding on the registration cards. The volunteers co-operated fully in giving the requisite facts, and the number of persons who refused to give information or whose data were so vague as to be useless was extremely small: in the industrial surveys, for instance, only 48 out of 12,906 (0.4%).

Results

The well-known fact that proportionately more men smoke than do women is supported by the figures given in Table I. Proportions for men were roughly twice the corresponding values for women. The maximum proportion of smokers among men was that for miners at Stoke, and the result for the pottery workers at Stoke was only slightly less than this maximum. Almost 70% of men in the Shropshire and

TABLE I.—*Proportions of Smokers of all Persons Interviewed*

Survey	Men			Women		
	Total Interviewed	No. of Smokers at Present	Percentage of Smokers	Total Interviewed	No. of Smokers at Present	Percentage of Smokers
Birmingham factory	5,821	3,840	66·0	1,859	700	37·7
Stoke miners ..	2,774	2,106	75·9			
,, potters ..	929	686	73·8	1,523	568	37·3
Shropshire ..	343	237	69·1	386	106	27·5
Herefordshire ..	1,760	1,039	59·0	2,222	626	28·2
Stourbridge ..	715	497	69·5	1,145	322	28·1

Stourbridge surveys were classed as smokers, as were two-thirds of the employees in the Birmingham factory. In contrast, the result for men in the Herefordshire group was outstandingly low, and it is interesting that this proportion was significantly less than that for Shropshire, which is also a rural area.

Table I also shows the almost identical proportion of smokers in women employed in the Birmingham factory and in female pottery workers, and the very close agreement between proportions of smokers in women who attended public surveys in Herefordshire, Stourbridge, and Shropshire, the majority of whom were not gainfully employed in industry or commerce.

In Table II, distinction is made between male cigarette and pipe smokers. The comments made above in respect of all male smokers regardless of method are appropriate to the proportion of cigarette smokers. The values for miners and potters were almost identical, and the differences in the other male groups were only small. The exception was Herefordshire, where only half of the men smoked cigarettes, but a greater proportion (10%) of men smoked pipes than in any other of our groups. The lowest proportion of pipe smokers was found in the potters of Stoke-on-Trent (5%).

TABLE II.—*Smoking Habits at Time of Survey by Age and Sex*

Age Group (Years)	Men				Women	
	Total Interviewed	Percentage of Cigarette Smokers	Percentage of Pipe Smokers	Percentage of Smokers All Types	Total Interviewed	Percentage of Cigarette Smokers
Birmingham Factory						
15–24 ..	1,327	47·8	2·3	50·1	767	31·0
25–34 ..	1,458	61·9	4·5	66·4	375	47·7
35–44 ..	1,334	65·4	8·0	73·4	363	43·3
45–54 ..	998	62·8	9·6	72·4	241	37·3
55 and over	704	56·4	15·1	71·5	113	31·8
All ages ..	5,821	59·0	7·0	66·0	1,859	37·7
Stoke Miners						
15–24 ..	423	65·9	1·2	67·1		
25–34 ..	648	77·3	2·5	79·8		
35–44 ..	646	72·9	7·1	80·0		
45–54 ..	668	69·0	8·2	77·2		
55 and over	389	50·9	19·0	69·9		
All ages ..	2,774	68·9	7·0	75·9		
Stoke Potters						
15–24 ..	165	53·3	1·2	54·5	499	27·7
25–34 ..	238	73·9	1·7	75·6	290	52·1
35–44 ..	236	73·3	5·1	78·4	336	49·7
45–54 ..	202	74·8	5·4	80·2	293	30·0
55 and over	88	59·1	19·3	78·4	105	22·9
All ages ..	929	68·9	4·9	73·8	1,523	37·3
Shropshire						
15–24 ..	45	37·8	2·2	40·0	84	19·0
25–34 ..	70	61·4	7·1	68·5	84	34·5
35–44 ..	101	75·2	4·0	79·2	93	43·0
45–54 ..	67	73·1	6·0	79·1	71	19·7
55 and over	60	50·0	13·3	63·3	54	13·0
All ages ..	343	62·7	6·4	69·1	386	27·5
Herefordshire						
15–24 ..	297	33·3	1·7	35·0	529	16·6
25–34 ..	401	54·9	5·5	60·4	440	40·9
35–44 ..	385	61·8	7·5	69·3	417	37·7
45–54 ..	324	51·6	14·2	65·8	390	36·2
55 and over	353	42·2	18·4	60·6	446	13·5
All ages ..	1,760	49·4	9·6	59·0	2,222	28·2
Stourbridge						
15–24 ..	98	46·9	2·0	48·9	250	22·0
25–34 ..	192	58·3	8·9	67·2	277	35·0
35–44 ..	198	67·7	8·1	75·8	304	37·8
45–54 ..	122	73·0	9·0	82·0	186	19·9
55 and over	105	50·5	16·2	66·7	128	14·1
All ages ..	715	60·7	8·8	69·5	1,145	28·1

As very little general information is available about the variations of current smoking habits according to age, we attach importance to the habits according to decennial age groups, also shown in Table II. Ages above 55 have been combined, as the number of persons over 60 years old was relatively small. The proportion of male smokers of all types for a given age group differed from one survey group to another. However, certain patterns emerge from Table II which are common to most, if not all, of the groups.

In the first place, a smaller proportion of men in the 15–24 age group were smokers than in any other age group, and the maximum proportions occurred for the two age groups 35–44 and 45–54 years. In all surveys except that of men in Stourbridge, differences between the values for these two age groups were very small. In each survey, smaller proportions of men aged 55 years and over were current smokers than in preceding age groups. Broadly speaking, values in this age group agreed closely with those for the age group 25–34 years.

A similar pattern of variation with respect to age was found when only male cigarette smokers were considered, although a much greater excess of cigarette smokers was found in younger men than in those aged 55 years and over. On the other hand, the proportion of men who smoked pipes increased with age; in each survey the proportion for men aged 55 years and over (45 years and over in the Herefordshire survey) was about twice that for the preceding age group.

The pattern of current smoking habits among women with respect to age differed considerably from that for men. Again several inter-survey differences are evident from Table II. In all age groups the proportions of smokers among female employees of the Birmingham factory and among female potters were higher than in the three other surveys. An exception was found in women aged 35–44 years in Shropshire, where only a relatively small number of women were interviewed, and the 45–54 years group in Herefordshire. Broadly speaking, greater proportions of women between 25–34 and 35–44 years smoked than did those at the lower and upper end of the age scale.

Smokers have been further analysed with respect to the number of cigarettes smoked a day, converting the amounts of pipe tobacco consumed per week into cigarettes a day according to the usual formula: 1 oz. (28 g.) of tobacco a week equals 4 cigarettes a day. Table III gives percentage distributions for each age group and each survey group. Examination of the distributions for *men of all ages* shows that the proportion smoking fewer than 5 cigarettes a day varied between 7.8 and 11.3%; there was a close correspondence between figures for the Shropshire and Herefordshire surveys. In three of the surveys slightly more than 40% of the men smoked 5–14 cigarettes a day, and there was close correspondence between two of the remainder; the proportion for the miners in Stoke was relatively high. There was therefore a large measure of agreement between the distributions for the surveys, although that for Stoke miners is atypical. Whereas the proportion of smokers was greater among miners than among men in any other survey group, the miners *consumed* less than smokers in the other groups. This finding reflects the fact that miners cannot smoke underground.

In each survey group the large proportion of *women* who smoked cigarettes consumed between 5 and 14 cigarettes a day. In two of the groups almost 30% smoked fewer than

TABLE III.—*Distribution of Smokers According to Age, Sex, and Number of Cigarettes (or equivalent pipe tobacco) Smoked a Day*

Age Group (Years)		Daily Consumption									
		Men					Women				
		<5	5–14	15–24	25 and Over	Totals	<5	5–14		25 and Over	Totals
Birmingham factory	15–24 ..	14·1	55·9	27·2	2·8	100·0 (666)	26·1	62·2	10·9	0·8	100·0 (238)
	25–34 ..	5·9	39·0	44·1	11·0	100·0 (969)	12·8	63·7	22·9	0·6	100·0 (179)
	35–44 ..	7·6	33·0	45·0	14·4	100·0 (979)	12·1	63·0	21·7	3·2	100·0 (157)
	45–54 ..	5·7	38·5	42·5	13·4	100·0 (723)	25·6	53·3	17·8	3·3	100·0 (90)
	55 and over	10·9	43·9	36·8	8·4	100·0 (503)	33·3	61·1	5·6	—	100·0 (36)
	All ages ..	8·4	40·9	40·1	10·6	100·0 (3,840)	19·9	61·6	17·0	1·5	100·0 (700)
Stoke Miners	15–24 ..	22·5	53·2	21·5	2·8	100·0 (284)					
	25–34 ..	7·5	45·5	39·9	7·2	100·0 (517)					
	35–44 ..	10·1	45·8	36·6	7·5	100·0 (517)					
	45–54 ..	9·3	47·9	35·9	7·0	100·0 (516)					
	55 and over	12·9	57·4	26·1	3·7	100·0 (272)					
	All ages ..	11·3	48·7	33·8	6·2	100·0 (2,106)					
Stoke Potters	15–24 ..	20·0	45·6	28·9	5·6	100·0 (90)	60·9	34·1	4·3	0·7	100·0 (138)
	25–34 ..	6·1	36·7	45·0	12·2	100·0 (180)	29·8	57·0	12·6	0·7	100·0 (151)
	35–44 ..	6·0	27·6	50·8	15·7	100·0 (185)	28·7	55·1	15·0	1·2	100·0 (167)
	45–54 ..	8·0	32·1	40·1	19·8	100·0 (162)	48·9	40·9	9·1	1·1	100·0 (88)
	55 and over	11·6	36·2	31·9	20·3	100·0 (69)	45·8	33·3	16·7	4·2	100·0 (24)
	All Ages ..	8·9	34·3	42·0	14·9	100·0 (686)	40·7	47·4	10·9	1·1	100·0 (568)
Shropshire	15–24 ..	11·1	33·3	55·6	—	100·0 (18)	31·3	43·8	18·8	6·3	100·0 (16)
	25–34 ..	8·3	33·3	47·9	10·4	100·0 (48)	31·0	55·2	10·3	3·3	100·0 (29)
	35–44 ..	7·5	28·8	51·3	12·5	100·0 (80)	22·5	55·0	22·5	—	100·0 (40)
	45–54 ..	3·8	37·7	41·5	17·0	100·0 (53)	14·3	64·3	14·3	7·1	100·0 (14)
	55 and over	13·2	34·2	39·5	13·2	100·0 (38)	42·9	28·6	—	28·6	100·0 (7)
	All ages ..	8·0	32·9	46·8	12·2	100·0 (237)	26·4	52·8	16·0	4·7	100·0 (106)
Hereford-shire	15–24 ..	8·7	47·6	37·9	5·8	100·0 (103)	30·7	56·8	10·2	2·3	100·0 (88)
	25–34 ..	7·9	44·0	39·8	8·3	100·0 (241)	19·4	61·7	16·7	2·2	100·0 (180)
	35–44 ..	4·1	39·6	43·7	12·7	100·0 (268)	13·4	59·9	24·2	2·5	100·0 (157)
	45–54 ..	8·0	39·0	36·2	16·9	100·0 (213)	17·0	57·4	22·0	3·6	100·0 (141)
	55 and over	11·7	50·9	29·0	8·4	100·0 (214)	18·3	51·7	25·0	5·0	100·0 (60)
	All ages ..	7·8	43·6	37·6	11·0	100·0 (1,039)	18·8	58·7	19·6	2·9	100·0 (626)
Stourbridge	15–24 ..	20·8	29·2	41·7	8·3	100·0 (48)	34·5	58·2	7·3	—	100·0 (55)
	25–34 ..	9·3	48·8	33·3	8·5	100·0 (129)	23·7	62·9	12·4	1·0	100·0 (97)
	35–44 ..	9·3	36·0	41·3	13·3	100·0 (150)	33·9	52·2	13·9	—	100·0 (115)
	45–54 ..	5·0	41·0	36·0	18·0	100·0 (100)	16·2	59·5	24·3	—	100·0 (37)
	55 and over	11·4	48·6	34·3	5·7	100·0 (70)	38·9	50·0	11·1	—	100·0 (18)
	All ages ..	9·9	41·5	37·2	11·5	100·0 (497)	29·2	57·2	13·3	0·3	100·0 (322)

5, and in another two groups almost one-fifth of the women smokers consumed only this amount. The exceptionally high proportion of women potters who smoked fewer than 5 a day may reflect the fact that smoking is restricted during certain phases of their work. Very few women smoked 25 cigarettes or more a day.

With regard to the age-specific variations in the amount of tobacco consumed, we found it difficult to specify an overall picture, as there are some marked inter-survey differences. Each survey is therefore summarized in turn. No comments are given for the Shropshire survey, as the numbers of smokers in individual age groups were rather small.

Inter-survey Differences

Birmingham Factory.—Few men between 15 and 24 years of age smoked 25 or more cigarettes a day, and a greater proportion of these young men smoked fewer than 15 cigarettes a day than did those in older age groups. The percentage distribution for the three age groups between 25 and 54 years was very similar. In the oldest age groups fewer men smoked more than 25 cigarettes than those in the preceding three groups. A quarter of the women smokers aged 15–24 years smoked fewer than 5 cigarettes a day. Women in the two groups between 25 and 44 years tended to smoke more than those in other age groups. The number of women in the oldest age group was small, but it is clear that such women smoked fewer cigarettes a day than did the younger women.

Potters.—The proportion of heavy smokers (more than 25 cigarettes a day) in men increased with age, and one-fifth of those aged 45 years and over smoked this amount. In the youngest age group almost two-thirds of the men consumed fewer than 15 cigarettes a day, and the corresponding proportion for the oldest age group was the second largest in this series. Between the ages 35 and 44 two-thirds of the smokers consumed 15 cigarettes or more a day. An outstandingly large proportion of women aged 15–24 years smoked fewer than 5 cigarettes and 95% in this group fewer than 15 a day. Similarly, as in the Birmingham factory, a close correspondence existed between the 25–34 and 35–44 age groups. Almost half of the women smokers aged 45 years or over smoked fewer than 5 cigarettes a day as compared with about 30% for those aged between 25 and 34 years.

Miners.—Consumption varied little with age between 25 and 54 years. Three-quarters of the youngest group smoked fewer than 15 cigarettes a day. The proportions of heavy smokers were small in both the youngest and oldest groups.

Herefordshire.—The proportion of heavy smokers in men increased from a minimum in the youngest to a maximum in the 45–54 years age group. Again a relatively large proportion of men over 55 years smoked fewer than 15 cigarettes a day. In this survey marked differences between consumption for the two youngest groups were not evident. Almost one-third of women in the youngest age group who smoked consumed fewer than 5 cigarettes a day. As elsewhere, the youngest women consumed fewer cigarettes than did female smokers of other ages. Distributions for the other age groups did not differ unduly from each other, although the proportion of smokers between 25 and 34 years who consumed 15 cigarettes a day or more was relatively low.

Stourbridge.—In the youngest age group exactly half of the male smokers consumed fewer than 15 cigarettes a day, and the value for these "light smokers" was highest in the oldest age group. With regard to heavy smokers, in

men the pattern was similar to that in the Herefordshire survey, with a sizable difference between the two oldest age groups. In this survey the total number of women smokers in each age group was somewhat small, and it is difficult to determine any definite age specific pattern.

Discussion

By collecting data at mass radiography surveys we arrived at our results in a very different way from most other authors who have studied smoking habits in this country in recent years. Some of these used, as controls of patients suffering or dead from carcinoma of the lung and chronic bronchitis, matched groups of residents in the same area, who for reasons of expediency and economy were chosen from in-patients and out-patients of general and specialized hospitals (Doll and Hill, 1950, 1952; McConnell *et al.*, 1952; Oswald *et al.*, 1953; Stocks and Campbell, 1955). One of these investigations (Lowe, 1956), is of particular interest to us, as that author's control group of in-patients and out-patients was drawn from the Birmingham area. Stocks and Campbell (1955) pointed out that "it is not known, and cannot be ascertained, to what extent, if at all, patients at general hospitals differ in respect of their past smoking habits from the whole population of the same age in the same area." Lowe's definition of smoking habits is different from that used by us in this paper, which deals only with current smokers, but there are certain indications that the smoking habits of his hospital patients may differ from those of industrial workers in Birmingham.

Well-known examples of investigations into the smoking habits of persons who at the time of questioning were neither confined to hospital nor attending out-patient clinics are the studies of doctors (Doll and Hill, 1954, 1956) and of civil servants in London (Oswald and Medvei, 1955). Both these occupations fell into an entirely different social group from the homogeneous groups in our surveys—the miners, potters, and electrical engineers. The Hulton Readership Survey (1956), based on 4,000 interviews of persons of 16 years of age and over, gives the proportion of those "who ever smoke a cigarette" as 65% for men and 42% for women, with an additional 17% of men "who ever smoke a pipe." This survey, like that of the doctors, was a nationwide investigation, and there may be sizable geographical differences hidden in national figures.

Our data may be compared with those given by Higgins (1957) in respect of a sample of the population in the Vale of Glamorgan, and with those given by Ogilvie and Newell (1957) for a control group of persons resident in Newcastle upon Tyne. Higgins found that 74% of men between the ages of 25 and 74 years were *current* smokers, as were 52% of women aged 25–44 years and 24% of women aged 45–74 years. By combining the results for our three public surveys and applying them to the age structure of Higgins's sample, we obtained the following corresponding proportions: men, 68%; women aged 25–44 years, 38%; women aged 45–74 years, 17%. Ogilvie and Newell found that 74% of men in their control series were current smokers, as were 28% of the women. Corresponding proportions for men and women in our three public surveys combined, after standardization with respect to age, were respectively 70% and 28%.

Conclusions

Differences between our findings and those of other writers may be due to the complex causes of response to mass radiography surveys. However, it seems highly unlikely that smoking habits contribute materially to the response and "lapse" rates at such surveys, and in these surveys the public had not been informed beforehand that questions about smoking would be asked.

In this investigation we attach importance to the following aspects:

(*a*) A smaller proportion of *men* aged between 15 and 24 years were smokers than in any other age group. There was relatively little change in smoking habits with age within the range 25–54 years, but the proportion of smokers among men aged 55 years and over was less than that for the preceding age group.

(*b*) The pattern of current smoking habits among women with respect to age was quite different from that for men. Proportions of smokers among women between 25 and 34 years and between 35 and 44 years of age were similar and greatly exceeded those referable to women in other age groups.

(*c*) The proportions of smokers among examinees in the industrial surveys were greater than those for persons examined at the public surveys, and such differences were especially noticeable for women.

(*d*) In addition to these differences between results obtained from the industrial and public surveys, there were variations within each of these two types of survey, and especially with regard to the amount of tobacco consumed. In particular, the findings for the men in the Herefordshire survey differed from those of the other two public surveys, and it would be of interest to compare the smoking habits of men in the same age and occupational groups in geographically neighbouring areas. For example, the smoking habits of North Staffordshire miners may differ from those of colliers in Lancashire (Higgins *et al.*, 1956), and this aspect will also be investigated.

We thank the staff of the three mass radiography units for their enthusiastic and painstaking work in recording information in addition to that normally obtained at M.M.R. examinations. Our thanks are also due to the Birmingham Regional Hospital Board for employing a temporary clerk to assist with the processing of the recorded data.

REFERENCES

Doll, R., and Hill, A. B. (1950). *Brit. med. J.*, **2**, 739.
—— —— (1952). Ibid., **2**, 1271.
—— —— (1954). Ibid., **1**, 1451.
—— —— (1956). Ibid., **2**, 1071.
Higgins, I. T. T. (1957). Ibid., **2**, 1198.
—— Oldham, P. D., Cochrane, A. L., and Gilson, J. C. (1956). Ibid., **2**, 904.
Hulton Readership Survey, 1956, Hulton Press, London.
Lowe, C. R. (1956). *Brit. med. J.*, **2**, 1081.
McConnell, R. B., Gordon, K. C. T., and Jones, T. (1952). *Lancet*, **2**, 651.
Medical Research Council (1957). *Brit. med. J.*, **1**, 1523.
Ogilvie, A. G., and Newell, D. J. (1957). *Chronic Bronchitis in Newcastle-upon-Tyne*. Livingstone. Edinburgh.
Oswald, N. C., Harold, J. T., and Martin, W. J. (1953). *Lancet*, **2**, 639.
—— and Medvei, V. C. (1955). Ibid., **2**, 843.
Posner, R. J. (1958). *Tubercle (Lond.)*, **39**, 38.
Stocks, P., and Campbell, J. M. (1955). *Brit. med. J.*, **2**, 932.

At a joint meeting of the Liverpool Medical Institution and the Manchester Medical Society on March 6, Dr. RALSTON PATERSON, director of the Holt Radium Institute, read a paper on "Breast Cancer: A Preliminary Report of Two Clinical Experiments." The value of simple *x*-ray castration was being studied on a series of 750 patients, and the five-year results for the first 300 were reported as a provisional finding. The overall figures showed a real advantage accruing from the use of *x*-ray castration in breast cancer. This had been more marked the earlier in the course of the disease that the radiation therapy was given. The second study, of the value of prophylactic post-operative irradiation, involved some 1,400 patients in all, and the results from 700 of these after five years were reported. These patients had been divided into four groups —i.e., those receiving and those not receiving quadrate radiation (primarily flap and axilla radiated), and those receiving and not receiving peripheral radiation (primarily supraclavicular and parasternal radiation). The results were effectively identical whether the patients were treated by irradiation prophylactically or merely carefully followed up and only irradiated if necessary. The second paper was by Mr. IAN ORR on "Surgical Surprises in the Small Intestine," in which he reviewed a number of lesions of the small intestine which might prove difficult to diagnose.

HAEMOGLOBIN E SYNDROMES IN A CEYLONESE FAMILY

BY

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Haemoglobin E is an abnormal type of human haemoglobin which appears to be the prototype in South-east Asia of sickle-cell haemoglobin in Africa. It was first reported in a North American child of partial Asiatic extraction (Itano, Bergren, and Sturgeon, 1954), and has since been shown to occur in Burma, Thailand, Malaya, Indonesia, Sarawak, Cambodia, and Bengal; single instances have been reported in a Persian and an Eti-Turk. In Ceylon it was first reported in the aboriginal Veddahs (Graff, Ikin, Lehmann, Mourant, Parkin, and Wickremasinghe, 1955), and further studies have shown that haemoglobin E also occurs in the general population, and it has been the only abnormal haemoglobin so far encountered in the island (de Silva, Jonxis, and Wickremasinghe, 1957).

The present paper is a report on a Sinhalese* family in Ceylon consisting of the parents and five children. The father carried the haemoglobin E trait, the mother was considered to have carried the thalassaemia trait, three of the children were found to be affected with thalassaemia–haemoglobin E disease, and two children were normal.

Methods and Materials

All blood counts were made on venous blood samples collected in Wintrobe mixture. Erythrocytes and platelets were counted, using pipettes, counting chambers, and coverslips conforming to A.H.T. Co. specifications. Haemoglobin was determined by the cyanhaematin method (Dacie, 1956). Haematocrit measurements were made in Wintrobe tubes after centrifugation at 3,000 revolutions a minute for 30 minutes. Reticulocytes were counted on fixed alcoholic brilliant cresyl blue preparations counterstained with Leishman's stain. Schumm's test, Coombs's test, and the staining for Heinz bodies and siderocytes were performed as described by Dacie (1956). Tests for sickling were done with sodium metabisulphite. Quantitative osmotic fragility was determined by the method of Dacie and Vaughan (Dacie, 1956), and serum bilirubin estimated as described by King (1946).

Haemoglobin types were identified by paper electrophoresis in 0.05 M barbitone buffer at *p*H 8.6, as well as in 0.05 M phosphate buffer at *p*H 6.5. Haemoglobin F was estimated by the alkali-denaturation test described by Singer, Chernoff, and Singer (1951). For confirmation of the haemoglobin types, blood samples were sent to Professor J. H. P. Jonxis, Department of Paediatrics, University of Groningen, The Netherlands.

*The Sinhalese are the majority community in Ceylon.

Case 1

G. T., a Sinhalese girl, aged 13, was admitted to the General Hospital, Colombo, in February, 1957, for continued fever of three months' duration, abdominal swelling, and marked dyspnoea. Her previous history revealed that she had suffered from shortness of breath and an abdominal swelling with distress in the left upper quadrant from the age of 2 years. She had been treated several times at her local hospital, as these symptoms were progressive. During this time she had also suffered from several bouts of fever with chills, rigors, vomiting, diarrhoea, and jaundice. Each attack lasted for about a week and recurred at intervals of two to three months.

On examination the patient was ill-nourished, apathetic, and extremely pale. Her temperature was 100.6° F. (38.1° C.), her height 4 ft. 2 in. (127 cm.), and her weight 54 lb. (24.5 kg.). She had a protuberant abdomen, wasted extremities, and a dry wrinkled skin. The conjunctivae were not icteric. There were no leg ulcers and the lymph nodes were not palpable. There was mild oedema of the ankles. The heart was enlarged and a soft grade II systolic murmur was heard at the apex. The liver was palpable three fingerbreadths below the right costal margin, was slightly tender and moderately firm, and had a smooth surface. The spleen was greatly enlarged, and extended 1 in. (2.5 cm.) below the umbilicus. It had a sharp edge, a smooth surface, and was not tender.

Laboratory Findings.—The urine showed a trace of albumin and bile salts, there was no sugar, and urobilin was detectable at a 1/20 dilution. Serum:—Total serum proteins were 6.4 g./100 ml. (albumin 2.37 g., globulin 3.72 g., fibrinogen 0.34 g.); serum bilirubin was 1.8 mg. per 100 ml.; icterus index 11 units; van den Bergh reaction direct delayed; Takata-Ara ++. Blood:—The findings are for the most part summarized in the Table; other findings were white blood cells 7,200 per c.mm., (68% polymorphonuclears, 32% lymphocytes); the blood picture showed anisocytosis, poikilocytosis, polychromasia, basophilic stippling, and hypochromia. Two attempts at marrow aspiration (sternum and iliac) were unsuccessful.

X-ray examination showed an enlargement of the heart, congestion of the lungs, and no abnormality of the skull and tubular bones; the hands showed rarefaction.

Haemoglobin:—No alkali-resistant fraction was detected, and paper electrophoresis revealed the presence of two components—one with the mobility of normal adult haemoglobin and the other with that of haemoglobin E.

Haematological Data

Case	Diagnosis	R.B.C. (mil./c.mm.)	Haemoglobin (g./100 ml.)	P.C.V. (%)	M.C.V. (μ^3)	M.C.H.C. (%)	Reticulocytes (%)	Platelets	Nucleated R.B.C.	Target Cells	Fragility
1. G.T.	Thalassaemia–haemoglobin E disease	0·85	2·1	8·5	100	25	17·2	42,000	0	0	0·38–0·32
2. C.T.	Normal "	2·93	6·6	23·0	78	29	2·8	162,000	+	+++	0·38–0·18
3. P.R.T.	"	4·22	11·1	35·0	83	33	0·5	76,000	0	0	0·50–0·26
4. B.M.T.	"	4·08	11·4	35·0	86	33	1·0	14,000	0	0	0·40–0·28
5. A.T.	Thalassaemia–haemoglobin E disease	3·50	6·9	31·0	89	22	4	12,100	+	+++	0·44–0·16
6. Mr. T.	Haemoglobin E trait ..	—	—	—	—	—	—	—	0	0	—
7. Mrs. T.	Thalassaemia trait.. ..	—	—	—	—	—	—	—	0	0	Cells resistant to haemolysis in distilled water

None of the blood samples showed sickling, malarial parasites, Heinz bodies, or siderocytes; Coombs's and Schumm's tests were negative in all cases.

Thalassaemia–haemoglobin E disease was diagnosed (see Discussion).

The patient had a low fever throughout her illness with an occasional rise in temperature accompanied by chills and rigors; the highest temperature recorded was 102° F. (38.9° C.). She had 12 blood transfusions—each of 250 ml. at weekly intervals—and was treated with penicillin for the fever. Her condition deteriorated, there being only a slight response to the transfusions, and she died three months after admission. The cause of death was thought to be congestive heart failure and an aplastic crisis due to congenital haemolytic anaemia. A necropsy was not performed.

Case 2

C. T., aged 10, brother of Case 1, with a history similar to hers, was admitted to hospital for an abdominal swelling of several years' duration.

On examination his height was 3 ft. 1½ in. (95 cm.) and his weight 48 lb. (21.8 kg.). He was pale, with a yellowish coloration of the skin. The conjunctivae were icteric and the cheek-bones high. The abdomen was protuberant. There were no active leg ulcers, but old scars were evident. Lymph nodes were not palpable. The heart was not enlarged and there were no murmurs. The liver edge was palpable three fingerbreadths below the right costal margin, and was firm but not tender. The spleen was grossly enlarged down to the level of the iliac crest; its surface was smooth, and it was not tender.

Laboratory Findings.—Urine:—Urobilin was present; there was no albumin, bile, or bile pigments. Serum:—Serum bilirubin was 6.8 mg. per 100 ml.; van den Bergh reaction, direct delayed; Takata-Ara ++; and the cephalin-cholesterol flocculation test +++. Blood:—The findings are for the most part summarized in the Table; other findings were: white blood cells, 4,200 per c.mm. (46% polymorphonuclears, 45% lymphocytes, 9% eosinophils); the blood picture showed anisocytosis, poikilocytosis, pessary forms, and microcytosis; there were many target cells and an occasional nucleated red cell (Fig. 1).

X-ray examination revealed trabeculations, which were most marked in the metacarpal bones, phalanges, and lower ends of the tubular bones; there were no changes in the skull.

Haemoglobin:—Alkali-resistant haemoglobin was significantly raised (5%), and paper electrophoresis revealed the presence of haemoglobin E and haemoglobin F.

On the above findings a diagnosis of thalassaemia–haemoglobin E disease was made. The patient was discharged from hospital and is attending school.

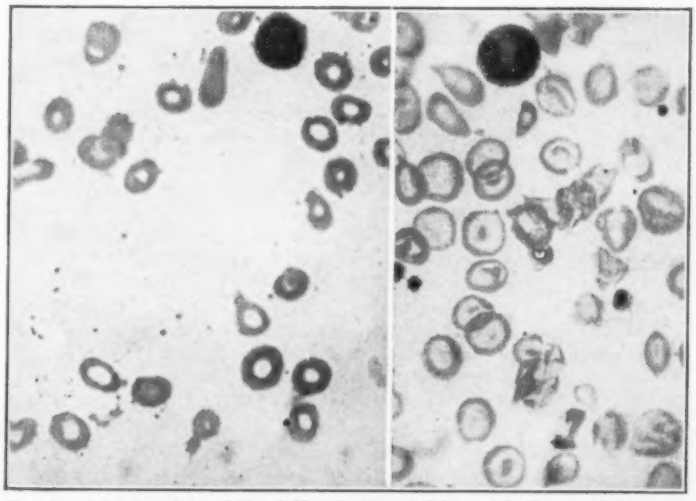

FIG. 1.—Stained peripheral blood films in Case 1 (left) and in Case 2 (right).

Family Study

Case 3.—P. R. T., a boy aged 7, the third in the family, had no history of anaemia, jaundice, chills, or rigors. Physical examination and laboratory studies revealed no abnormalities. The blood findings are summarized in the Table. The haemoglobin was normal.

Case 4.—B. M. T., a girl aged 6, the fourth in family, was similar to Case 3.

Case 5.—A. T., a girl aged 4, the youngest in the family, had no history of definite illness, but presented suggestive signs. She was pale and her conjunctivae were icteric. The heart was not enlarged, the liver was palpable 1½ fingerbreadths below the right costal margin, and the spleen was not palpable. The blood findings are summarized in the Table. *X*-ray examination showed trabeculations in the metacarpals and phalanges of both hands. Haemoglobin:—Alkali-resistant haemoglobin was significantly increased and paper electrophoresis showed haemoglobins E, A, and F. Thalassaemia–haemoglobin E disease was diagnosed.

Case 6.—Mr. T., aged 40, the father, had no symptoms of a haemoglobinopathy, and physical examination showed no abnormalities. Haemoglobin:—No alkali - resistant haemoglobin was present, but paper electrophoresis revealed the presence of haemoglobins E and A. He was regarded as an asymptomatic carrier of haemoglobin E trait.

Case 7.—Mrs. T., aged 40, the mother, gave a history which revealed no untoward features. The blood picture was not unusual, but her red blood cells were found to be resistant to lysis in distilled water. Haemoglobin:—No alkali-resistant or abnormal haemoglobins were present, but she is considered to be a carrier of the thalassaemia trait (see Discussion).

Discussion

No studies have been made of the relative prevalence of haemoglobin A_2 and haemoglobin E among the Ceylonese. This is unfortunate, since these haemoglobins are indistinguishable by paper electrophoresis in barbitone buffer at *p*H 8.6 or phosphate buffer at *p*H 6.5. However, quantitative measurements indicated that haemoglobin A_2 constituted 1.8 to 3.5% of the total haemoglobin in a series of 26 individuals studied by Kunkel and Wallenius (1955). In the cases described here, the amount of the slow-moving haemoglobin component was at a rough estimate much higher than this figure, and was accordingly identified as haemoglobin E.

Case 1 presented unusual features. Paper electrophoresis and a negative alkali-denaturation test indicated that she carried the haemoglobin E trait; she was severely affected and ultimately died. These observations are contrary to those of Chernoff, Minnich, Na-Nakorn, Tuchinda, Kashemsant, and Chernoff (1956), that haemoglobin E in the trait form is associated with an entirely benign asymptomatic carrier state. In their series of 30 individuals with haemoglobin E trait, who were apparently free from other incidental diseases, there was no consistent history of anaemia, cardio-respiratory distress, jaundice, leg ulcers, or arthralgias, and the haematological findings were not unusual. However, in our Case 1, although the haematological findings, except for the evidence of severe anaemia, were normal, the patient had been physically incapacitated from the age of 2 years with progressive anaemia, attacks of jaundice, chills, fever, shortness of breath, and hepatosplenomegaly. Hence, although haemoglobin F was not detectable by the alkali-denaturation test, hers is most probably a case of thalassaemia–haemoglobin E disease in view of the clinical picture, the fatal anaemia, and the fact that carriers of the haemoglobin E trait are symptomless or show only mild

symptoms. Alternatively, she might have been a case of haemoglobin E trait (or even thalassaemia trait) with anaemia due to some entirely different cause.

Case 2 had haemoglobin E and about 5% haemoglobin F in his blood and showed signs of severe anaemia. He was evidently a case of thalassaemia–haemoglobin E disease, but the relatively low figure of 5% is in contrast to the values of 20–40% obtained in Siamese by Chernoff (quoted by Lehmann, 1957). The absence of demonstrable haemoglobin A is in keeping with the findings of other workers that the presence of the thalassaemia gene interferes with the expressivity of the gene responsible for the production of haemoglobin A.

Cases 3 and 4 were unaffected and showed only haemoglobin A in their bloods. It follows that neither of the parents of this family could be homozygous for either the haemoglobin E gene or for the gene (or genes) responsible for thalassaemia. Analysis of the parents' bloods showed the presence of haemoglobins E and A in the father, and only haemoglobin A in the mother. Hence the appearance of haemoglobin F in Cases 2 and 5 may have been due either to a mutation or to inheritance from one of the parents.

The suggestion of mutation is a purely academic one, since all indications are that mutation from a normal gene

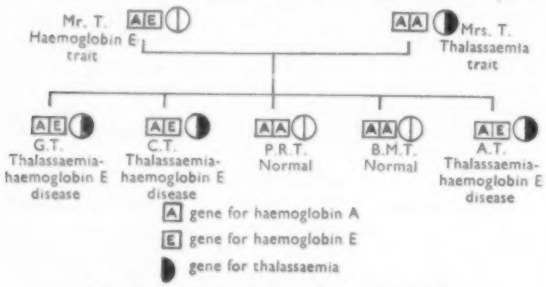

FIG. 2.—Genetic representation of the family.

to abnormal at any given locus takes place only once in 100,000 gametes, so that it is only in cases like those of the ABO and MN groups, where most members of families have been tested, or in congenital diseases like haemophilia, where the resulting disease has striking manifestations, that instances of human mutation may be expected to be found. Moreover, the presence of two separate identical mutations in a single sibship is extremely unlikely and would occur in only one in 10,000,000,000 families for each gene. Hence one of the parents in the family studied must have been a carrier of the thalassaemia gene. It is perhaps reasonable to infer that the gene is present in the mother, because had it been present in the father he would have shown at least some of the rather severe manifestations of thalassaemia–haemoglobin E disease. We therefore regard the mother as a carrier of the thalassaemia trait with non-penetrance of the thalassaemia gene: that she was not entirely normal was indicated by the increased resistance of her red blood cells to haemolysis. Accordingly we have constructed the genetic table as illustrated in Fig. 2.

A possible racial origin of haemoglobin E cannot be ascertained as yet. This abnormal haemoglobin probably arose in South-east Asia as the result of a single mutation and was then disseminated from this focus. With regard to Ceylon, the Sinhalese as well as the Veddahs are of partial Bengali extraction, and it is possible that the haemoglobin E found in Veddahs and Sinhalese originated in Bengal.

Mackey and Vivarelli (1954) suggested that sicklers are more prone to develop falciparum malaria than non-sicklers. Allison (1954) and Raper (1955) reported statistically significant differences in the incidence of malaria in carriers of the sickle-cell trait and those without the trait. Others (Moore, Brass, and Foy, 1954; Archibald and Bruce-Chwatt, 1955) could not confirm the differences. No statistical investigation has been done so far to determine whether carriers of haemoglobin E were more resistant to malaria than those without haemoglobin E. Na-Nakorn, Minnich, and Chernoff (1956) reported that haemoglobin E offered no protection against malaria. Still, it is interesting to note that the incidence of haemoglobin E in Ceylon is largely confined to areas which had been hyperendemic for malaria prior to 1945 (de Silva *et al.*, 1957).

Summary

Clinical, haematological, and genetic manifestations of haemoglobin E syndromes in a Ceylonese family are described. In this family, the father carried the haemoglobin E trait, three children were affected with thalassaemia–haemoglobin E disease, whilst the mother and two other children showed only normal adult haemoglobin in their bloods.

Our thanks are due to Professor P. B. Fernando and to Dr. H. Gunawardene for permission to publish their cases; to Professor C. C. de Silva, Dr. D. B. Gunasekera, and the Director of the Medical Research Institute for their encouragement and criticism in the preparation of this paper; and to Professor J. H. P. Jonxis for confirming the identification of the haemoglobins.

REFERENCES

Allison, A. C. (1954). *Brit. med. J.*, **1**, 290.
Archibald, H. M., and Bruce-Chwatt, L. J. (1955). Ibid., **1**, 970.
Chernoff, A. I., Minnich, V., Na-Nakorn, S., Tuchinda, S., Kashemsant, C., and Chernoff, R. R. (1956). *J. Lab. clin. Med.*, **47**, 455.
Dacie, J. V. (1956). *Practical Haematology*, 2nd ed., pp. 31, 74, 95-132. Churchill, London.
de Silva, C. C., Jonxis, J. H. P., and Wickremasinghe, R. L. (1957). "Haemoglobinopathies in Ceylon," presented at the Symposium on Abnormal Haemoglobins at Istanbul, September, 1957.
Graff, Jean A. E., Ikin, Elizabeth, W., Lehmann, H., Mourant, A. E., Parkin, Dorothy M., and Wickremasinghe, R. L. (1955). *J. Physiol. (Lond.)*, **127**, 41P.
Itano, H. A., Bergren, W. R., and Sturgeon, P. (1954). *J. Amer. chem. Soc.*, **76**, 2278.
King, E. J. (1946). *Micro-analysis in Medical Biochemistry*, 1st ed., p. 42. Churchill, London.
Kunkel, H. G., and Wallenius, G. (1955). *Science*, **122**, 288.
Lehmann, H. (1957). *Practitioner*, **178**, 198.
Mackey, J. P., and Vivarelli, F. (1954). *Brit. med. J.*, **1**, 276.
Moore, R. A., Brass, W., and Foy, H. (1954). Ibid., **2**, 630.
Na-Nakorn, S., Minnich, V., and Chernoff, A. I. (1956). *J. Lab. clin. Med.*, **47**, 490.
Raper, A. B. (1955). *Brit. med. J.*, **1**, 1186.
Singer, K., Chernoff, A. I., and Singer, L. (1951). *Blood*, **6**, 413.

FRAMYCETIN IN INFANTILE GASTRO-ENTERITIS DUE TO PATHOGENIC ESCHERICHIA COLI

BY

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Framycetin sulphate ("soframycin") is an antibiotic produced by a strain of *Streptomyces* which was isolated by Decaris in 1947 (Decaris, 1953). Given parenterally, this substance is highly toxic to the kidneys and the eighth cranial nerves (Massénat-Deroche, 1954), a fact which has retarded its clinical use. When given by mouth, however, it is harmless at the prescribed dosage levels, since it is very poorly absorbed from the gut.

In vitro its action on various strains of pathogenic *E. coli* is far superior to that of chloramphenicol and the tetracyclines. It is both bacteriostatic and bactericidal (Massénat-Deroche, 1954).

Various investigators have reported on its usefulness in infective infantile gastro-enteritis (Marquézy *et al.*, 1955; Laplane *et al.*, 1955; Cathala *et al.*, 1954; Schneegans *et al.*, 1955, 1956; Boyer and Tissier, 1955; Pierret *et al.*, 1956; Shidlovsky *et al.*, 1955–6).

Several of us (Hainaut *et al.*, 1957) have already reported on the effectiveness of neomycin in the treatment of gastro-enteritis due to pathogenic *E. coli*. In the present paper we have endeavoured to compare the activity of framycetin with that of neomycin, using the same experimental conditions and applying identical criteria.

Material

Our trials of framycetin were carried out on the one hand during a local epidemic due to *E. coli* O.55:B5 in the premature babies' wing of the Clinique Pédiatrique Universitaire, and, on the other, on a group of infants admitted for gastro-intestinal disturbances. We report only on the cases in which bacteriological investigation confirmed the presence of pathogenic *E. coli* in the stools.

We have used framycetin in the form of a flavoured water-soluble powder. Daily doses, divided into two portions, varying from 125 to 250 mg., were given according to the patients' weight (50 mg./kg.). This treatment was administered for 3 to 12 days. Generally a five-day course was sufficient. For three gastro-intestinal cases we had to combine framycetin with chloramphenicol by mouth for various associated infections (otitis, bronchopneumonia, pyelonephritis).

Twenty-five infants were treated. Their ages ranged from 7 days to 7 months and their weights from 1,400 to 6,900 g. Of these, 14 were premature babies (from 1,400 to 2,200 g.) and 8 others were undernourished.

Culture of the stools, before treatment, yielded the following results: *E. coli* O.55:B5 in 20 cases, *E. coli* O.26:B6 in 2 cases, *E. coli* O.119:B9 in 2 cases, *E. coli* O.111:B4 in 1 case.

How gravely ill these babies were can be gauged from the severity of the diarrhoea and dehydration, which we graded as follows: 14 infants passed numerous watery stools (more than eight daily), whereas in 11 cases the stools had the same character but were less frequent; 15 infants presented with moderate dehydration; 10 infants were very dehydrated—amongst these, five showed severe neurotoxicity.

Results

In order to assess the results of treatment and compare them with our trials with neomycin, we adopted the same criteria as before—that is: (1) the time taken to clear the pathogenic agent from the stools (bacteriological examinations were carried out before and repeatedly during treatment by the Institut Provincial de Bactériologie); and (2) clinical considerations: (*a*) the rate of disappearance of dehydration, (*b*) the time required for the stools to become normal in number and appearance, and (*c*) the duration of vomiting.

1. Culture of the stools became negative within three days in 22 babies and within five days in 2. Only one remained positive after five days' treatment. This infant's stools were still positive for *E. coli* O.55:B5 six weeks later, but there was no sign of gastro-enteritis.

2a. In most cases the fluid balance was restored by drinking. Only five children received intravenous infusion because they were in a highly toxic state. Apart from a single infant who continued to be in that state for 72 hours, all were normally hydrated after 48 hours.

2b. The gastro-intestinal disturbances recovered rapidly. The stools returned to normal within 48 hours in 18 infants. After 72 hours only one still had diarrhoea; he was a premature baby whose stools remained soft and granular for 12 days in spite of prolonged therapy and negative stool cultures. The stools resumed their normal appearance in this case only after a concomitant urinary infection had been cured, the latter having caused periodic bouts of fever. Another infant, who had improved rapidly in 36 hours, relapsed on the fourth day of treatment; this case was cured in turn by neomycin therapy.

2c. Administration raised no problem. No digestive upset resulted. Of 12 infants who had severe vomiting at the start, in only 2 did it not subside within 24 hours. After 48 hours all vomiting had ceased, and in no case did it recur during treatment.

To find out whether framycetin might be nephrotoxic, we carried out extensive urine analyses and made several estimations of the blood urea level, both during and after treatment; all readings were strictly normal.

Conclusion and Summary

Framycetin has a very favourable action on gastro-enteritis due to pathogenic *E. coli* in premature babies and in infants. Our investigations were mainly concerned with *E. coli* O.55:B5. Framycetin is well tolerated and does not appear to be toxic at the dosage used—50 mg. per kg. per day by mouth for five days as an average. It acts with the same speed and potency as neomycin, which we have used in gastro-enteritis caused by *E. coli* O.111:B5 and O.55:B5. Diarrhoea, dehydration, and vomiting disappear very rapidly and often after two days' treatment; stool cultures usually become negative within three days.

Acknowledgment is gratefully made to Laboratoires Roussel for kindly placing soframycin at our disposal for this trial; we are also indebted to the staff of the Institut Provincial de Bactériologie, who carried out the examination of the patients' stools.

BIBLIOGRAPHY

Boyer, J., and Tissier, M. (1955). *Brux.-méd.*, **35**, 1224.
Cathala, J., Poupinet, S., Janet, L., and Naudot, A. (1954). *Nourrisson*, **42**, 198.
Decaris, L. J. (1953). *Ann. pharm. franç.*, **11**, 44.
Hainaut, H., Lambrechts, A., and Malchair, R. (1957). *Sem. méd. prof. méd.-soc.*, **33**, 1669.
—— —— —— Fredericq, P., Betz-Barreau, M., Lafontaine, A., and De Maeyer-Cleempoel, S. (1956). *Acta paediat. belg.*, **10**, 177.
Lafontaine, A., Lambrechts, A., De Maeyer-Cleempoel, S., and Hainaut, H. (1956). Ibid., **10**, 197.
Lambrechts, A., Hainaut, H., and Nicolas-Goldstien, M. (1957). *Presse méd.*, **65**, 1607.
Laplane, R., Debray, P., and Duché, D. J. (1955). *Arch. franç. Pédiat.*, **12**, 861.
Lutz, A. (1955). *Strasbourg méd.*, **116**, 338.
—— and Hofferer, M. J. (1954). *Presse méd.*, **62**, 1282.
Marquézy, R. A., Debray, P., Leveau, J., Grenier, B., and Lepage, M. (1955). *Arch. franç. Pédiat.*, **12**, 859.
Massénat-Deroche, B. (1954). Thesis (Paris): "La Framycétine, un nouvel antibiotique."
Pierret, R., Breton, A., Gaudier, B., and Prouvost, J. M. (1956). *Lille méd.*, **1**, 99. Abstract in *Presse méd.*, 1956, **64**, 1365.
Schneegans, E., Haarscher, A., and Lévy, M. (1956). *Arch. franç. Pédiat.*, **13**, 106.
—— Lutz, A., Rohmer, A., Haarscher, A., and Lévy, M. (1955). Ibid., **12**, 424.
Shidlovsky, B. A., Marmell, M., and Prigot, A. (1955-6). *Antibiotics Annual*, p. 118.

The need to advance our knowledge of mental health and illness was urgent, said Viscount MONCKTON at the meeting of the Mental Health Research Fund on March 25. Nearly half our hospital beds were occupied by the mentally sick, and mental sickness constituted by far the greatest problem of medicine to-day. An advance in knowledge in this field would do more towards the happiness of mankind than any other improvement in the standard of health or of living. Nevertheless he must say that the interest which had been stimulated in the subject had not been matched by corresponding generosity in voluntary gifts from the public generally. No doubt the sum spent on research in the field of defence and in scientific work for peaceful purposes was enormously greater than that spent on medical research. And it would be easy to criticize the Government for not devoting more of what could be spent on research to medical research. But he had been too lately released from the Government stable to be ready to make that sort of criticism without going on to say what research now being done should be abandoned to make way for this. There were limits to what the Government could spend, even on medical research.

TUBERCULIN SENSITIVITY IN KUWAITI SCHOOLS

BY

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The occurrence of infection with tuberculosis—and consequently a positive tuberculin reaction—was accepted a generation ago as a normal event of childhood. With the more recent antituberculous campaigns, a large number of persons escaped infection in their childhood, and now there are large communities in which the majority of young adults have also escaped infection. The rates of tuberculin sensitivity in children were found to have fallen steadily in the last 50 years, especially in communities in which the mortality from tuberculosis has declined.

Kuwait, on the Persian Gulf, is a recently established community. It was formed less than three hundred years ago, mostly from Arabs and to a less extent Persians. It has always been a rural community. With the discovery of oil in the last few years, it started to acquire the characters of an urban community.

The number of inhabitants in Kuwait is under 230,000. Over 60% of these are "foreigners" arriving after the discovery of oil. The number of "indigenous" Kuwaitis is about 80,000. In the last few years Kuwait has shown a very marked progress in many aspects of modern civilization. There are 61 schools, 15,000 boy students and 10,000 girl students. Over 80% of the students are "indigenous" Kuwaitis and less than 20% are "foreigners."

Present Investigation

A total of 1,348 schoolboys and 652 schoolgirls were examined. All of them were indigenous Kuwaitis. They ranged in age from 5 to 15 years.

Method.—The intracutaneous Mantoux test was used. Injections of 0.1 ml., containing 0.0002 mg. of P.P.D.—that is, 10 I.U.—were given intracutaneously on the anterior surface of the left forearm. The results were read 72 hours later. A reaction was regarded as positive when there was an area of infiltration measuring 6 mm. or more in diameter. Erythema without infiltration was disregarded. The results are shown in Tables I and II.

TABLE I.—*Percentage of Positive Reactors to* 0.0002 *mg. of P.P.D.*

Years:	5	6	7	8	9	10	11	12	13	14	15	Mean
Males ..	12·8	13·2	13·8	15·4	19·2	20·2	26·6	30·6	35·5	46·1	58·3	21·2
Females ..	8·0	10·3	12·0	14·3	14·7	13·6	15·9	16·6	25·9	37·5	42·9	15·0
Total	10·6	12·4	13·4	15·0	16·0	17·4	22·2	25·4	31·0	44·1	54·8	19·2

TABLE II.—*Percentage of Severe Reactions with Infiltration 20 mm. or More in Diameter*

	M	F	Total
Severe reactions among total students examined	5·2	2·7	4·4
" " " positive cases ..	23·8	20·0	22·9

Discussion

The results of tuberculin surveys vary widely from place to place and from time to time. In Vienna, for example, in 1908, 95% of the population were positive tuberculin reactors at 12 years, while in some recent surveys in Australia the percentage did not exceed 1.9 at the same age. Variations in susceptibility to tuberculous infection in various persons or in various communities depend on many factors, notably the influence of race and heredity, undernourishment, industrialization, poverty, overcrowding, etc.

The results of the tuberculin test for Kuwaiti students show that the percentage of positive reactors is relatively low till the age of 10 years (17.4); then it gradually rises to 25.4 at the age of 12, after which it increases very rapidly to reach 54.8 at the age of 15 (Table I). The percentage of positive reactors is definitely higher in males than in females during the age period of 5 to 15 years.

In spite of the environmental and nutritional factors which favour the spread of tuberculous infection in Kuwait, the incidence of the infection seems to be relatively low. Habits such as using common cups for drinking-water or coffee, eating with the fingers, spitting on the ground, and kissing the nose as a sign of respect are prevalent, although education will have, and undoubtedly is having, a marked effect. Also there is much dust and a high humidity—exceeding 95% in many days of the summer. The Kuwaiti diet is mostly soup and boiled rice; eggs, milk, cheese, fresh fruits, and vegetables are scarce. The diet is definitely deficient in proteins, fats, and vitamins. In a medical examination of 500 Kuwaiti students, over 40% were found to have clinical evidence of vitamin-A deficiency, and 70% gave a history of a definite protein deficiency. Another important factor is the great number of immigrants into Kuwait in the last few years. Many of them are badly off workers—mostly coming from Persia—and are living under the worst conditions of dirt, poverty, overcrowding, and physical exhaustion. The extent of tuberculous infection in this group has not yet been studied.

In spite of the above-mentioned deleterious factors—which would undoubtedly facilitate the spread of tuberculous infection—the incidence of tuberculous disease in Kuwait can be regarded as low. In a survey done on 8,414 Kuwaiti students of 5 to 15 years of age, 0.39% of the boys, and 0.17% of the girls showed tuberculous lesions on mass miniature radiography. The percentage for the whole group was 0.24. This low incidence of tuberculosis in the presence of the above-mentioned factors seems paradoxical but may be due to the fact that overcrowding in bedrooms is uncommon. During hot weather, which prevails throughout the greater part of the year, the Kuwaitis have the habit of sleeping in open places—either on the roof or in the house-yard. The efficient medical service and the free treatment available in the last few years encourage most of the people to attend at the various clinics for routine examination. Cases of disease are thus spotted at an early stage and patients have a chance of a full and gratuitous treatment. Whether the racial factor has a role in this low incidence cannot be evaluated.

Table I shows that the percentage of positive reactors rises rapidly after the age of 12 years. The percentage of negative reactors is relatively high below that age. Therefore the tuberculin test can be of value in diagnosis, as regards the Kuwaiti students, only below the age of 12; and after that its diagnostic value rapidly diminishes.

Summary and Conclusion

A tuberculin survey on 2,000 Kuwaiti students was made, using 0.0002 mg. of P.P.D. intracutaneously.

The percentage of positive reactors was found to be relatively low, especially under the age of 12 years.

The percentage of positive reactors was higher in males than in females.

The turberculin test may be of diagnostic value in Kuwaitis only below the age of 12 years.

I wish to thank the Minister of Health, H.E. Sheikh Fahd Al Salim Al Sabah, for permission to publish this paper. I am grateful to Dr. M. A. Abboud, Dr. E. Parry, Dr. B. Yassin, and Dr. G. Ramadan for their invaluable help.

BIBLIOGRAPHY

Abboud, M. A., and Abdin, Z. H. (1954). *Gaz. Egypt. paediat. Ass.*, **2**, 71.
Bicknell, F., and Prescott, F. (1946). *The Vitamins in Medicine*, 2nd ed. Heinemann, London.
Clarke, B. R. (1952). *Causes and Prevention of Tuberculosis*. Livingstone, Edinburgh.
Faber, K. (1938). *Acta tuberc. scand.*, **12**, 287.
Hart, P. D'Arcy (1932). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 164.
Preventive Medicine Dept. (1957). Reports of Antituberculosis Section. P.H.D., Kuwait.
—— (1957). Reports of School Health Section. P.H.D., Kuwait.
Yelton, S. E. (1946). *Publ. Hlth Rep. (Wash.)*, **61**, 1144.

BEMEGRIDE ANALEPSIS

BY

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The article by Dotevall and Herner (1957) has prompted us to summarize some recent pharmacological observations concerning the safe and widespread analeptic activity of bemegride to hypnotics both structurally related and unrelated to it.

Bemegride (β-methyl-β-ethylglutarimide) will wake mice from moderately deep acute hypnosis (ready response to pain, moderate depression of corneal reflex, sleeping time 60–80 minutes) due to such structurally related hypnotics as barbiturates (pentobarbitone), thiobarbiturates (thiopentone), glutarimides (glutethimide; "doriden", and others), diketopiperidines (methyprylone; "noludar"), diketotetrahydropyridines ("persedon"), diketothiazanes ("dolitrone"), diketothiazolidines (5:5-diethyl-2:4-diketothiazolidine), monoureides (carbromal and bromvaletone), and succinimides (5-methyl-5-phenylsuccinimide and others) (Shaw, Simon, Cass, Shulman, Anstee, and Nelson, 1954; Shulman, 1956; Somers, 1956; Frey, Hushahn, and Soehring, 1956; Kimura and Richards, 1957; Shulman and Laycock, 1957a, 1957b). It also antagonizes such structurally unrelated hypnotics as substituted acetamides (phenyl-diethylacetamide), saturated and unsaturated alcohols (chlorbutol, methylpentynol, "placidyl"), aldehydes (chloral hydrate), carbamates (urethane), cyclic ethers (paraldehyde), and sterols ("viadril") (Frey *et al.*, 1956; Kimura and Richards, 1957; Shulman and Laycock, 1957c). Its effect on deep acute hypnosis (minimal response to pain, marked depression of corneal reflex, frequent cyanosis and death, sleeping-time 2–12 hours) due to these drugs has been indicated by Kimura and Richards (1957) and Shulman and Laycock (1958). Further, bemegride will antagonize morphine-induced respiratory depression but not hypnosis or analgesia in the rabbit and dog (La Barre, 1957; La Barre, Dumont, and Desmarez, 1957; Shulman and Laycock, 1957c).

Clinical antagonism has been reported to such drugs as pentobarbitone, thiopentone, glutethimide, methyprylone, persedon, primidone, carbromal, and bromvaletone, either alone or occasionally combined with structurally unrelated hypnotics (Shulman, Shaw, Cass, and Whyte, 1955; Harris, 1955; Holten, 1956; Palmer, 1956; von Planta and Klingler, 1956; Dotevall and Herner, 1957).

A current quantitative investigation of this problem in mice (Shulman and Laycock, unpublished observations) indicates that at moderate levels of hypnosis the analeptic activity of bemegride to structurally related hypnotics is confined between much narrower limits than that shown to structurally unrelated hypnotics. Bemegride is generally a more potent analeptic to this latter class of substance.

We wish to emphasize the high margin of safety associated with the administration of bemegride in the relief of moderate hypnosis induced by both classes of drugs. Significant reduction in sleeping-time ($p \leq 0.001$) has been obtained by the administration of mildly convulsant doses of bemegride (20 mg./kg. each 15 minutes) to mice narcotized with hypnotics of 15 structurally different types. A few transient and minimal signs of toxicity have been occasionally observed in the case of only two drugs (urethane and β-methyl-β-*n*-amylglutarimide).

The administration of convulsant doses of bemegride (60 mg./kg. stat. and up to 6 doses of 30 mg./kg. at seven-minute intervals) to mice deeply narcotized with the same series of structurally diverse hypnotics also resulted in a significant decrease in sleeping-time ($p \leq 0.001$) in the majority of cases (carbromal, chloral hydrate, 5:5-diethyl-2:4-diketothiazolidine, dolitrone, methyprylone, methylpentynol, paraldehyde, pentobarbitone, persedon, phenyldiethylacetamide, placidyl, and viadril). Transient and mild signs of toxicity (tremors and Straub tail) followed awakening from such hypnosis due to chloral hydrate, 5:5-diethyl-2:4-diketothiazolidine, dolitrone, and phenyldiethylacetamide.

Antagonism was less pronounced and toxicity more marked in the case of deep hypnosis due to urethane, glutarimide, and succinimide. At slightly higher doses of these hypnotics bemegride treatment resulted in early antagonism (corneal reflex and response to pain), followed by respiratory depression and death preceded, in the case of urethane, by severe convulsions. This potentiation was greatest in the case of β-methyl-β-*n*-amylglutarimide, which, like bemegride, is a β,β-disubstituted glutarimide.

These results support the advisability of gradual titration of analeptic against hypnotic under strictly supervised conditions in an endeavour to keep the animal in the "safe state" (Shulman *et al.*, 1955).

Although great care should be exercised in too freely extrapolating the results of these laboratory investigations to the treatment of clinical cases, it is hoped that these observations may be helpful to the clinician faced with the diagnosis and treatment of the patient in coma, particularly where self or accidental administration of hypnotics may be suspected as the underlying cause. The careful intravenous administration of bemegride (up to three 50-mg. doses at intervals of 5 to 10 minutes) would appear to be a safe and useful diagnostic and possibly therapeutic aid, especially in the young patient in whom the likelihood of cerebrovascular accident may be anticipated to be minimal and preliminary investigation of whom has rendered the diagnosis of acute metabolic disturbance unlikely.

The value of bemegride in the diagnosis of an epileptiform focus has been previously indicated (Delay, Verdeaux, Verdeaux, Drossopoulo, Schuller, and Chanoit, 1956). Additional aspects of bemegride activity have been reviewed by Shaw (1957).

REFERENCES

Delay, J., Verdeaux, G., Verdeaux, J., Drossopoulo, G., Schuller, E., and Chanoit, P. (1956). *Presse méd.*, **64**, 1525.
Dotevall, G., and Herner, B. (1957). *Brit. med. J.*, **2**, 451.
Frey, H. H., Hushahn, E. E. W., and Soehring, K. (1956). *Arzneimittel-Forsch.*, **6**, 583.
Harris, T. A. B. (1955). *Lancet*, **1**, 181.
Holten, C. (1956). *Ugeskr. Læg.*, **118**, 72.
Kimura, E. T., and Richards, R. K. (1957). *Arch. int. Pharmacodyn.*, **110**, 29.
La Barre, J. (1957). Ibid., **110**, 465.
—— Dumont, J., and Desmarez, J. J. (1957). Ibid., **110**, 452.
Palmer, K. N. V. (1956). *Brit. med. J.*, **1**, 1219.
von Planta, P., and Klingler, M. (1956). *Schweiz. med. Wschr.*, **86**, 691.
Shaw, F. H. (1957). *Med. J. Aust.*, **1**, 712.
—— Simon, S. E., Cass, N., Shulman, A., Anstee, J. R., and Nelson, E. R. (1954). *Nature (Lond.)*, **174**, 402.
Shulman, A. (1956). *Austr. J. exp. Biol. med. Sci.*, **34**, 471.
—— and Laycock, G. M. (1957a). Ibid., **35**, 421.
—— —— (1957b). Ibid. In press.
—— —— (1957c). Ibid. In press.
—— —— (1958). Ibid. In press.
—— Shaw, F. H., Cass, N. M., and Whyte, H. M. (1955). *Brit. med. J.*, **1**, 1238.
Somers, T. C. (1956). *Nature (Lond.)*, **178**, 996.

RENAL INSUFFICIENCY IN TERMINAL RESPIRATORY FAILURE

BY

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AND

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Patients dying of pulmonary failure have shown evidence of a functional renal failure with elevated blood urea (Simpson, 1957). This is not a matter which we have particularly studied, and indeed the general condition of these patients precludes extensive metabolic investigation; but in an experience of 24 patients admitted to this unit with cor pulmonale we have come across two whose terminal illness was accompanied by significant suppression of urinary output. Diminished renal plasma flow and glomerular filtration rate are of course well recognized in patients with cor pulmonale, even when the cardiac output is high (Davies and Kilpatrick, 1951; Lewis *et al.*, 1952); but we have not found any reports or recognition that anuria is likely. Acute renal failure complicating cor pulmonale may be one of those conditions which escape notice by lurking between the accepted territories of two specialties; at any rate, it is mentioned neither in the cardiological textbooks of Friedberg (1956) and Wood (1956) nor in the equally excellent monograph of Merrill (1955) on renal failure.*

Case 1

A woman aged 20 had had cough, with copious purulent sputum, from infancy; she had had spasmodic dyspnoea from the age of 4, and her activity had always been restricted. Dyspnoea on exertion had been prominent at the age of 18, and cyanosis and finger-clubbing were first noticed then. At the age of 19 she had been admitted to hospital with pyrexia and congestive heart failure, which improved with antibiotics, salt restriction, and mercurial diuretics; she remained cyanosed, breathless, and tired until her final admission to hospital on November 2, 1952, under the care of Dr. H. T. Howat. Since August, 1952, she had been confined to bed with dyspnoea and oedema, and had been on a low-salt diet, with injections of organic mercurials, to which there had been a good diuretic response until November 1, when she was given a mercurial injection, but passed no urine until admission the next day. She was treated conservatively by intragastric drip of glucose and arachis oil, the total daily intake of fluid being one litre (Bull, Joekes, and Lowe, 1949). She passed only a few ounces of urine each day until November 10, when a moderate diuresis began, and continued until her death from respiratory failure, on November 22, in spite of treatment with antispasmodics, antibiotics, and oxygen.

During the oliguric period her blood urea rose to 158 mg./100 ml. on November 10, and had fallen to 76 mg./100 ml. on the 13th. Her plasma sodium was 139 mEq/l. on November 6, and 141 on the 10th; but on the 13th, after diuresis had begun, it rose to 151 mEq/l. Her urine at this stage was of low specific gravity (1002) and contained albumin; the electrolyte content was low (Na, 5 mEq/l.; Cl, 9 mEq/l.; and K, 17 mEq/l.), although she was probably water-depleted from inability to drink sufficient fluid. Her plasma CO_2 was not increased (25 and 27.5 mEq/l. on November 6 and 10); her chloride was somewhat low (95 and 94 mEq/l.). Phosphate and organic acids were not determined. Her plasma potassium was 6.5 mEq/l. on November 9, but had fallen to 3.6 mEq/l. the next day. On November 19, when she had been passing urine for over a week but was terminally ill, the plasma sodium was 130 mEq./l.; and the plasma potassium 7 mEq./l.

At necropsy (Dr. B. L. Williams) she was found to have very extensive bronchiectasis involving the whole of the right lung, and the left lower lobe, with a terminal bronchopneumonia. The right ventricle was grossly dilated and hypertrophied, and there was hepatic congestion, and some free fluid in the abdomen. The kidneys were not enlarged, and showed no macroscopic changes. The microscopical appearances in the kidney were as follows: Small foci of slight round-cell infiltration of boundary zone; occasional tubules show dilatation and irregular thinning of epithelium and a very few contained desquamated necrotic cells and polymorphs; no sign of epithelial regeneration; this picture is that of acute tubular necrosis of minimal degree (many nephrons show widespread fine vacuolation of tubular cytoplasm, ? fatty, ? hydropic, without any sign of necrosis).

Case 2

A man of 44 had a 20-year history of cough and breathlessness, with an episode of "pneumonia" 15 years before his death and a transient haemoptysis four years before death. He was admitted to hospital on November 11, 1952, after collapsing in the street. He had noted increasing breathlessness and swelling of the ankles for two months.

On admission he was apathetic, cyanosed, and breathless, with sacral and ankle oedema. There were scattered crepitations in both lungs, but no dullness was found. He was given penicillin and treated in an oxygen tent. On November 12 he passed urine after a test dose of 0.5 ml. of a mercurial diuretic; but after a dose of 2 ml., the next day he became and remained anuric, until his death on the evening of November 14. On that day his blood urea was 78 mg./100 ml.; plasma sodium 138 mEq/l.; and potassium 7 mEq/l. He had a leucocytosis of 44,200/c.mm., with 94% polymorphs.

Necropsy (Dr. B. L. Williams) showed a chronic bilateral tuberculous bronchopneumonia with caseation, many acid-fast bacilli, and scattered foci of polymorphonuclear infiltration indicating a secondary pyogenic infection. The right ventricle was dilated and hypertrophied, and the liver showed centrilobular congestion and necrosis. The bladder was empty. The kidneys were slightly enlarged (right 200 g., left 210 g.), but the capsule stripped easily, and the cortex and medulla were moderately differentiated. The right kidney had a small demarcated caseous focus in one of the pyramids. On microscopical examination no abnormality was seen (apart from some fine vacuolation of tubular epithelium—? fatty, ? hydropic).

Discussion

The main cause of death in these two patients was advanced pulmonary disease, with cardiac failure. The first patient died at an unusually early age, from very extensive bronchiectasis; she had passed through an anuric episode, from which she was recovering. The second patient, with an infected tuberculous bronchopneumonia, was terminally anuric. The most likely mechanism to account for acute renal failure in association with cor pulmonale is a further substantial reduction in an already low renal blood flow. Each of these patients was specifically noted to have cold extremities, a weak radial pulse, and a systolic blood pressure of 100 mm. Hg. It can be inferred that they had passed into the low-output advanced stage of cor pulmonale (Wood, 1956). In Case 1 the clinical course and necropsy findings are consistent with the hypothesis that the patient had an episode of ischaemic acute tubular necrosis; the second patient died before the full course of this disorder could be clinically manifest. Both patients had been given mercurial diuretics, but in the second the amount given was only 0.5 and 2 ml.; and neither patient showed the renal lesion of a mercurial nephropathy.

*Since writing the above, we have found the possibility of anuria referred to by Stuart-Harris and Hanley (1957) in these terms: "A severe oliguria or anuria with resulting uraemia may be seen terminally."

Although mercury salts in large amounts can cause a full-blown tubular necrosis, the effect of small amounts of mercurials, such as are in question here, is to produce an epithelial necrosis limited to the proximal tubule and not involving the basement membrane (Oliver *et al.*, 1951). The first patient had had a full course of mercurials while on a low-salt diet, so that iatrogenic sodium depletion is a possible additional cause of lowered renal blood flow; against this possibility is the absence of hyponatraemia in the early anuric stage, and the restoration of urine flow spontaneously, while on a sodium-free intake. Arterial desaturation may well aggravate the effects of renal ischaemia; but hypercapnia is probably not a critical factor, as it was absent in the first patient. We have not observed anuria in other forms of cardiac failure.

In the last few days of illness both patients had hyperkalaemia (7 mEq/l.); one had a definitely low plasma sodium (130 mEq/l.) and the other a low-normal value (138 mEq/l.). We have recently seen another patient with terminal cor pulmonale, but without anuria, whose plasma sodium was 130 mEq/l. and potassium 7.6 mEq/l. Anoxia and acidosis are recognized causes of a shift of potassium from cells to extracellular fluid; so that the obvious explanation of hyperkalaemia in terms of diminished renal output of potassium may be less important than internal shifts of potassium, and possibly also of sodium. This is a question which could only be settled by full balance-studies, which are not likely to be made. It is relevant, however, to mention that Moore *et al.* (1954), studying other types of acute renal failure, found that patients whose total exchangeable potassium was low quite often had a high plasma potassium; and one of us (D. A. K. B.) has seen a patient with corrosive sublimate poisoning whose plasma potassium fell from 8 to 3.5 mEq/l. in 24 hours, during which time metabolic acidosis had been corrected by infusion of 200 ml. of molar sodium lactate.

Acute renal failure occurring in such circumstances may well be regarded as almost the least of a patient's troubles; while it constitutes an additional therapeutic problem, the situation may sometimes be met by conservative treatment, which is more likely to succeed if the condition is promptly recognized. More important, perhaps, than the treatment of established renal failure is the recognition that it can occur in patients with lung disease, whose cor pulmonale has been complicated by a lowering of cardiac output, often associated with acute respiratory infection. These observations perhaps reinforce in some small degree the already strong case for the prompt and vigorous treatment of suspected acute respiratory infection in patients with bronchitis and emphysema; in this way, the dangerous situation of peripheral circulatory failure may be prevented or cut short.

Summary

Two patients with terminal respiratory failure had in addition acute oliguric renal failure; in one the urine flow returned before death, while the other died before this could happen. It is suggested that a terminal fall in cardiac output in patients with cor pulmonale may on occasion produce ischaemic tubular necrosis.

We are grateful to Professor R. Platt and Dr. H. T. Howat for allowing us to describe their cases; and to Professor A. C. P. Campbell for reviewing the renal histology.

REFERENCES

Bull, G. M., Joekes, A. M., and Lowe, K. G. (1949). *Lancet*, **2**, 229.
Davies, C. E., and Kilpatrick, J. A. (1951). *Clin. Sci.*, **10**, 53.
Friedberg, C. K. (1956). *Diseases of the Heart*, 2nd ed. Saunders, Philadelphia.
Lewis, C. S., Samuels, A. J., Daines, M. C., and Hecht, H. H. (1952). *Circulation*, **6**, 874.
Merrill, J. P. (1955). *The Treatment of Renal Failure*. Grune and Stratton, New York.
Moore, F. D., Edelman, I. S., Olney, J. M., James, A. H., Brooks, L., and Wilson, G. M. (1954). *Metabolism*, **3**, 334.
Oliver, J., MacDowell, M., and Tracy, A. (1951). *J. clin. Invest.*, **30**, 1307.
Simpson, T. (1957). *Lancet*, **2**, 105.
Stuart-Harris, C. H., and Hanley, T. (1957). *Chronic Bronchitis, Emphysema, and Cor Pulmonale*, p. 129. Wright and Son, Bristol.
Wood, P. (1956). *Diseases of the Heart and Circulation*, 2nd ed. Eyre and Spottiswoode, London.

MEPROBAMATE IN THE TREATMENT OF STUTTERING

BY

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Speech defects are common, affecting 3–10% of children. Surveys such as those analysed by McAllister (1937) and Burt (1937) have shown an incidence of approximately 1% of stuttering in schoolchildren. The aetiology of stuttering is complex. Klingbeil (1939) quotes Charles Bell (1773–1842), professor of anatomy at Edinburgh, as attributing the condition to a choreiform affection of fluency of speech. Many have considered it a conflict for dominance between the cerebral hemispheres for control of the speech mechanism. Various other theories have been propounded.

Stuttering is an expressive disorder of communication the tendency to which is probably present from the beginning of development of speech. As the child grows in age a complexity of factors adds a reactionary overlay, a major factor being the disorder of speech itself. In the adult, methods of speech therapy are inseparable from psychotherapy to relieve anxiety and tension.

In view of the handicap which stuttering presents, the application of drugs which allay states of anxiety merits consideration. We decided to apply meprobamate in support of the accepted methods of speech therapy.

Clinical Results

Eighteen patients were selected for treatment. All were severely affected by stuttering and had been treated by speech therapy previously, with little improvement, at this and other centres. Secondary tonic or secondary tono-clonic stuttering was present in all cases. They all had defects in social adjustment.

Results of Treatment

No.	Sex	Age	Occupation	Drug Dosage Tablets per Day	Response to Treatment
1	M	18	Van driver	3	No improvement
2	M	19	Draughtsman	3–6–8	Slight improvement
3	M	23	Compositor	3	Good
4	M	24	Joiner	3–6	,,
5	F	24	Housewife	3	,,
6	M	25	Butcher	3	Very good
7	M	26	Printer	3	,, ,,
8	M	26	Railway fireman	3–6	Good ,,
9	F	28	Catering trade	3	,,
10	M	28	Architect	3–4–6	,,
11	M	29	Draughtsman	3	,,
12	M	29	Engineer	3	Slight improvement
13	M	31	,,	3–6	Good
14	M	34	Compositor	3	Very good
15	M	37	Post Office worker	3	,, ,,
16	M	39	Wood-working machinist	3	,, ,,
17	M	42	Technical manager	3	,, ,,
18	M	50	Storeman	3	No improvement

Very good = Extent of improvement such that speech difficulty appears only during exceptional emotional tension. Good = Subjective and objective improvement permitting satisfactory employment as indicated, with intermittent speech hesitancy.

The patients were seen at intervals of one week during active treatment and later at intervals of one month. The period of such supervision was eight months. Meprobamate was used in tablets of 400 mg.; one tablet three times a day was employed initially, and in some cases this dosage was increased according to effect. The results of treatment are summarized in the Table.

It will be seen that a very good result was obtained in six patients (33%), a good result in eight (44%), and little or no improvement in four (22%). The dosage used is shown in the Table. For most patients one tablet thrice daily was adequate.

Control tablets of identical appearance and similar taste were used in the management of eight patients. Two claimed some subjective response, but the other six said they were ineffective, although they were questioned and examined in a group having active drug treatment. Following active drug therapy it was possible to substitute control tablets with continued benefit to a variable extent. No useful result followed institution of meprobamate dosage in the absence of speech therapy.

Case Reports

The response obtained is illustrated in the following case histories.

Case 10.—An architect aged 28 had stuttered since being frightened by a dog when he was 3 years old. His stutter was of the secondary tonic type. He had good insight into his speech difficulty and quickly learned to control his blocks in "bland" speech situations where he was subjected to little tension. The nature of his work caused him anxiety in many situations requiring the giving of precise information. The resultant tension made his attempts to exert control over his blocks ineffective and he stuttered very badly. He was given three meprobamate tablets a day. The effect was minimal, and daily dosage was increased to four and then six tablets. Drowsiness appeared in the late afternoon, so the dose was reduced to four tablets a day. He then gained in speech confidence because of diminution in tension enabling control of his blocks. At the time of writing he was using the tablets only when required in difficult speech situations. He felt no impairment of the concentration required for his work on the optimum dose of four tablets a day.

Case 2.—A draughtsman aged 19 had had a stutter since he was a child. It was now of the secondary tonic type, and was characterized by very severe tension in the speech musculature during a block, so that his tongue protruded and the corners of his mouth were depressed. He was much concerned about his stutter and tried to use the methods of control which he had been taught. Most of his attempts were abortive because of the extreme tension present. The effective dosage of meprobamate was six tablets a day, upon which he felt generally relaxed, but the specific tension in his speech muscles was not much attenuated. He was better able to use control, but results were so equivocal that the meprobamate was discontinued.

Case 6.—A butcher aged 25 had a secondary tonic stutter. He felt a particular focus of tension in his chest when having a block. The stutter was a great handicap at his work in a butcher's shop, as when busy he was often unable to speak because of extreme tension. Speech therapy proved helpful, but he was still unable to cope with the ordeal of dealing with his blocks when trying to talk to customers. He was given three meprobamate tablets a day, and felt a marked improvement in his ability to stay relaxed under all speech conditions. His control of blocks steadily improved. This was accompanied by an increase in self-confidence. Eventually he was able to dispense with the tablets and still maintain a marked speech improvement.

Discussion

Meprobamate has been used widely in the treatment of anxiety and nervous tension. Turvey (1956) has reported that 60% of psychoneurotic and other patients with tension and tremors derive benefit from a dosage of four to six tablets a day. Electromyographic studies by Dickel *et al.* (1956) have shown a relaxation which was still more pronounced in patients with severe neuromuscular hyperactivity. Gillette (1956) has examined this relaxant action in a wide range of musculo-skeletal and neurological disorders, and comments upon the greater value of skilled observation than attempts at control measures in assessment. In agreement with this, we have examined a carefully selected series of patients who had enjoyed minimal improvement during previous treatment; the assay of their progress has been based upon clinical experience to a greater extent than upon attempted strict control.

Stuttering is characterized by clonic and tonic interruptions in the breath stream, in a state of neuromuscular tension. Progression into adult life is accompanied by distortion of the personality, and few adults suffering from this condition are free from hypersensitivity regarding their disability. The extent to which it prejudices their employment and social status cannot be minimized.

Treatment of the adult stutterer is often disappointing and is usually protracted. A further limitation is the shortage of qualified speech therapists. The report of the Advisory Council on Education in Scotland (1951) on establishment for speech therapy is still to be implemented, and facilities are limited at most hospitals. A drug which facilitates speech therapy and shortens the duration of treatment is therefore of special value. Meprobamate has been found very useful for this purpose. No toxic effects were observed among our patients. The Council on Drugs of the American Medical Association (1957) has commented upon an incidence of toxic reactions, mainly involving individual hypersensitivity, but it still appears to be a comparatively safe drug to use. The object in using a drug of this type is to interrupt the vicious circle of tension, speech inhibition, and consequent anxiety. By accomplishing this, patients become more accessible to speech therapy, and a better result can be obtained in suitable cases than by the application of normal methods over a longer period. The importance of the psychological factor is demonstrated by the possibility of maintaining a proportion of the patients upon a placebo once the useful action of the drug has been demonstrated. It is a practical procedure to permit the individual patient to adjust his dosage according to circumstances as they arise, using the drug in certain instances for a protracted period in small intermittent dosage at discretion, thereby avoiding relapse.

Summary

Stuttering is a common condition and occasions severe handicap. Facilities for speech therapy are limited. Meprobamate is useful in relaxing the state of tension which provokes and perpetuates the condition. It has been found to be of value in restoring speech confidence, facilitating treatment, and shortening the period of speech therapy required.

We are indebted to Dr. John B. Gaylor, consultant neurologist to the Western Infirmary, Glasgow, for his kind encouragement and advice, and to John Wyeth and Brother Limited for provision of the meprobamate and control tablets.

REFERENCES

Advisory Council on Education in Scotland (1951). *Pupils Handicapped by Speech Disorders*. H.M.S.O., Edinburgh.
Burt, C. (1937). *The Backward Child*. University of London Press.
Council on Drugs, American Medical Association (1957). *J. Amer. med. Ass.*, **164**, 1332.
Dickel, H. A., Dixon, H. H., Wood, J., and Shanklin, J. G. (1956). *West. J. Surg.*, **64**, 197.
Gillette, H. E. (1956). *Int. Rec. Med.*, **169**, 453.
Klingbeil, G. M. (1939). *J. Speech Dis.*, **4**, 115.
McAllister, A. H. (1937). *Clinical Studies in Speech Therapy*. University of London Press.
Turvey, S. E. C. (1956). *Canad. med. Ass. J.*, **74**, 863.

The late Sir James Walton, F.R.C.S. (1881–1955), was an expert on precious metals and gems, and at the time of his death was president of the National Association of Goldsmiths and chairman of the Gemmological Association. These bodies have now jointly established the Sir James Walton Memorial Library, one of the most comprehensive private libraries on jewellery, gemmology, gold and silverware, and horology. A brief description of it is published in the *Journal of Gemmology*, 1958, **6**, 223.

Medical Memorandum

Hypoglycorrhachia in Meningeal Carcinomatosis

A low sugar content in non-purulent cerebrospinal fluid is usually regarded as being due to tuberculous meningitis. Berg (1953) described three cases of meningeal gliomatosis with a decreased glucose content in the cerebrospinal fluid and collected from the literature 46 cases of diffuse leptomeningeal tumour, including melanoma, reticuloses, and sarcoma, in which the sugar estimate was recorded; 33 showed levels less than 40 mg./100 ml., which Berg regarded as the lower level of normal. Eighteen of the 46 cases were meningeal carcinomatosis, of which 17 had a sugar content of under 50 mg./100 ml.

Since Berg's article eight further instances have been recorded, and it may be noted that two are described in the British literature (Murphy, 1955; Reiseger, 1956).

The following case is reported to stress the importance of the glucose content of the cerebrospinal fluid in this condition.

CASE REPORT

A 49-year-old married woman was admitted to hospital on June 24, 1955. Her symptoms had started around December, 1954, with fronto-vertical headache occurring irregularly throughout the day eased by aspirin and worsened by coughing and stooping. She vomited approximately twice daily from January to March, 1955; low backache was present since April, and this extended to frequent left sciatic pain. Intermittent diplopia for periods up to two days was present for three weeks, and she noticed herself making irrelevant statements during a conversation.

Her past history disclosed that she had been attending the chest clinic since March 18, 1952, for a mass *x*-ray finding of a small, probably inactive, shadow in the right upper lobe.

Neurological examination showed marked ataxic gait, right abducent paresis, dysdiadokokinesis of the left hand, and straight-leg raise bilaterally limited to 70 degrees from the horizontal by sciatic pain. The left leg showed weakness of the calf and anterior tibial muscles, with an absent knee-jerk, vibration sense was impaired, pain sensation was diminished, and cerebellar ataxia was present.

Chest *x*-ray examination revealed a large circular opacity in the right upper zone; an electroencephalogram showed "considerable slow activity of moderate voltage in the left temporal area; the slow activity is focal and is consistent with the presence of a cerebral lesion." Bronchoscopy: "Lesion is too peripheral for visualization but is probably bronchial carcinoma." A ventriculogram was normal. The cerebrospinal fluid findings are shown in the Table. Guinea-pig inoculation was negative.

Cerebrospinal Fluid Findings

Date	Cells per c.mm.	Polys. %	Lymphocytes %	Protein	Sugar	Chloride
				mg. 100 ml.		
Aug. 3	121	38	62	300	22	650
,, 5	64	39	61	180	37	644
,, 6	64	26	74	180	32	639
,, 7	85	26	74	180	27	643
,, 8	84	26	74	180	36	633
,, 9	62	21	79	180	28	643
,, 10	28	28	72	—	18	658
,, 16	25	53	47	350	11	620
Sept. 2	46	45	55	400	13	629

Intramuscular streptomycin, 1 g. daily, with oral isoniazid, 300 mg. daily, was given until her death. During August some neck stiffness appeared, the left leg lower motor neurone lesion increased, hypotonia was evident in the other limbs, vision in the left eye was blurred, and a bilateral eighth-nerve deafness became apparent. At the beginning of September she was unable to sit up unsupported because of dizziness; headache and photophobia were prominent. Both legs were very weak and wasted, with absent tendon reflexes and normal plantar responses; posterior column sensation was now normal, the straight-leg-raise test was increasingly painful and there was diminished pain sensation and absent touch sensation in L 5, S 1, and S 2 segments. Dysphagia was frequent and urinary retention became evident. The patient was very somnolent, with noisy intervals, and lay on her back with marked neck rigidity. Death occurred on October 13.

Necropsy Findings.—A well-differentiated adenocarcinoma was present in the upper lobe of the lung with secondaries in the regional lymph nodes. There was no macroscopic evidence of intravertebral metastasis; the meninges were opalescent and showed a diffuse adenocarcinomatous infiltration.

Berg (1953) collected all cases of meningeal carcinomatosis in which the cerebrospinal fluid glucose level was mentioned and found it to be normal in only one instance. McCormack *et al.* (1953) described six cases of metastatic meningeal carcinomatosis with abnormally low cerebrospinal fluid sugar levels. Meissner (1953) described four cases of meningeal carcinomatosis; in two of these the C.S.F. glucose was estimated to be 24 mg./100 ml. Rogers and McDermott (1954) recorded a single case of this disease in which low glucose levels showed considerable fluctuation; this variation is shown in many of the cases reported. Fischer-Williams *et al.* (1955) reviewed the literature on carcinomatosis of the meninges and described three further cases; in one instance the C.S.F. sugar content was 50 mg./100 ml. Reiseger (1956) notes a case with a sugar level of 44 mg./100 ml. Similarity to tuberculous meningitis is commented on in several case reports (Dodge *et al.*, 1952; Rogers and McDermott, 1954; Murphy, 1955).

Theories to explain the hypoglycorrhachia include increased glycolytic rate of tumour cells and mechanical blockage of the blood/cerebrospinal fluid barrier by the growth. Warburg and Minami (1923) have shown that carcinomatous cells *in vitro* rapidly metabolize glucose. Glucuronidase and lactic acid have been found in large quantities in neoplastic effusions of the pleura and peritoneum (Fishman *et al.*, 1950), and Meissner (1953) comments on the fact that such an analysis has not been done on the C.S.F. in meningeal carcinomatosis. Goldring and Harford (1950) showed that a low C.S.F. sugar in a bacterial meningitis could not be accounted for by the metabolic activity of the organisms and the leucocytes. Sifontes *et al.* (1953) demonstrated a decreased absorption of glucose from the blood to the C.S.F. in cases of tuberculous meningitis.

In the case reported it was thought initially that the pulmonary lesion was either a bronchial carcinoma with multiple neurological metastases or intracranial metastases with a polyneuritis due to neoplasm. The diagnosis of tuberculous meningitis secondary to a pulmonary tuberculoma was also entertained but was thought unlikely until the hypoglycorrhachia was demonstrated.

Our thanks are due to Dr. C. E. Kellett for permission to report this case and to Mr. L. P. Lassman for his valuable assistance.

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REFERENCES

Berg, L. (1953). *Neurology*, **3**, 811.
Dodge, H. W., Sayers, G. P., and Svien, H. J. (1952). *Proc. Mayo Clin.*, **27**, 259.
Fischer-Williams, M., Bosanquet, F. D., and Daniel, P. M. (1955). *Brain*, **78**, 42.
Fishman, W. H., Markus, R. L., Page, O. C., Pfeiffer, P. H., and Homburger, F. (1950). *Amer. J. med. Sci.*, **220**, 55.
Goldring, S., and Harford, C. G. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **75**, 669.
McCormack, L. J., Hazard, J. B., Gardner, W. J., and Klotz, J. G. (1953). *Amer. J. clin. Path.*, **23**, 470.
Meissner, G. F. (1953). *Cancer*, **6**, 313.
Murphy, E. F. (1955). *Lancet*, **1**, 231.
Reiseger, F. (1956). *Brit. med. J.*, **1**, 572.
Rogers, W. E., and McDermott, W. (1954). *Amer. Rev. Tuberc.*, **69**, 1029.
Sifontes, J. E., Williams, R. D. B., Lincoln, E. M., and Clemons, H. (1953). Ibid., **67**, 732
Warburg, O., and Minami, S. (1923). *Klin. Wschr.*, **2**, 776.

Reviews

TEXTBOOK OF OBSTETRICS AND GYNAECOLOGY

Combined Textbook of Obstetrics and Gynaecology for Students and Practitioners. Edited by Dugald Baird, B.Sc., M.D., D.P.H., F.R.C.O.G. Sixth edition. (Pp. 936+xii; illustrated. 95s.) Edinburgh and London: E. and S. Livingstone Ltd. 1957.

To reduce the size of a textbook by a third would not be inherently difficult, but to make this change in a book that was already good and by this drastic reduction make it even better is a major achievement. It says a great deal for the skill and ingenuity of its editor, Professor Dugald Baird, that the new sixth edition of the *Combined Textbook of Obstetrics and Gynaecology*, though nearly 500 pages smaller than its predecessor, is such excellent value. In his preface the editor pays tribute to the four famous men who wrote the first edition in 1923—Munro Kerr, Haig Ferguson, James Hendrey, and James Young. Of these, only Professor James Young is a contributor to the new edition. He has written the chapters dealing with pelvic anatomy and with the factors and phenomena of labour.

At a time when the Sassenachs might be pardoned for thinking that the Scots are a nation divided in dispute over the kilt and the trews, it restores a sense of perspective to see the unity of which 17 eminent contributors are capable. This edition is so well edited that it has none of the disadvantages often seen in textbooks written by multiple authors. The production of the book leaves little to be desired. It is convenient in size. The paper is pleasant to handle and contributes much to the general excellence of the illustrations, which are lavishly used throughout. So great is the visual appeal of beautiful clear pictures that they can be dangerous unless chosen very carefully. For example, the criticism made of the last edition for depicting myomectomy through a posterior-wall incision for fibroids which could be removed as easily and more safely by the anterior route still applies. It is doubtful whether the contribution the book can make to students and practitioners would be decreased if the already sketchy account of gynaecological operations was omitted. Many readers will think the omission would be an improvement. The danger of good illustrations giving false ideas is further demonstrated in the excellent reproduction in Fig. 448 of the uterogram without tubal filling. The caption draws attention to the rounded cornua of "total occlusion subsequent to criminal abortion." The interstitial tube may be organically occluded with the remaining tube perfectly healthy, but the differential diagnosis of an identical picture due to functional occlusion should be mentioned, or the half-truth taught by the illustration may result in some unfortunate patient being subjected to unnecessary surgery.

In discussing the treatment of genital tuberculosis on page 730 the dose of streptomycin and P.A.S. is expressed in grains instead of grammes—obviously a genuine proof-correcting error and not a lapse into homoeopathy. Occasionally guidance on important issues is lacking, or so brief as to be of little value. For example, "women who are poor surgical risks should have an artificial menopause induced by radium or *x* rays." The student may well ask, in these days of careful pre-operative preparation, skilled anaesthesia, and improved surgical techniques, what constitutes a poor-risk patient and what are the arguments against radium as well as for it. Just half a page is allowed for discussion of "failed forceps," and the surprising conclusion reached that if spontaneous delivery does not occur after an injection of morphine and scopolamine, and if an easy forceps delivery is not then possible, a further attempt at forceps delivery "may be made," but if this fails "there is no alternative but to undertake a craniotomy." There is little of practical value in this short section to help the practitioner in trouble, but there is some excuse in the final statement that the detailed discussion of the management of these cases "is more suitably dealt with in a textbook for specialists." Some of the space used for the description of subtotal hysterectomy, sterilization, or presacral sympathectomy could perhaps be better used in giving more detailed advice on how to safeguard both the infant and the mother in those admittedly difficult cases which can lead to a "failed forceps." The way in which the orthodox teaching has been modified by new ideas is well illustrated in the wise advice given on the uses of radiography in obstetrics and the useful chapter on psychological aspects of midwifery and gynaecology. This is a very good book which can be warmly recommended.

J. STALLWORTHY.

OBESITY

Obesity: Its Cause, Classification, and Care. By E. Philip Gelvin, M.D., F.A.C.P., and Thomas H. McGavack, M.D., F.A.C.P (Pp. 146+xi. $3.50.) New York: Hoeber-Harper. 1957.

This is by far the best book on obesity that has so far appeared, though in so controversial a field this judgment should be understood to mean only that I agree with most of what is written in it. Another reviewer might not. Most, but not all. Although we find such heartening statements as "calories are not mentioned" and "people like to eat food, not calories," there is a little too much stress laid on calories in the book as a whole; too little stress, perhaps, on the fact that some people can eat *x* calories and stay thin while others eating the same amount get fat. No one denies that fat comes from food, but no useful purpose is served by looking upon "vital statistics" as the product of a simple profit-and-loss account: it so evidently is not. The writers know this is a fallacy, but it is a pity they have not applied to its exposure the enthusiasm with which they have exposed the even commoner mistakes that obesity is due to hypothyroidism or hypopituitarism. They are perhaps a little infected by that lack of proper humility which seems to be an occupational disease of writers on obesity, a tendency to pretend to an understanding which we still do not have, even to disregard facts which do not fit neatly into a simple explanation. They dismiss, for instance, the fact that many obese women have pitting oedema over their shins by a simple denial that it is so. One feels, too, that they are occasionally dazzled by the magic of "the literature," accepting statements as true just because they have been published.

On the practical side there is too little stress on the advantages of a high-protein diet, which is curiously described as "monotonous and unpalatable"—a remark which could emanate only from gastronomic philistines. The real disadvantage of this diet is that it is expensive, but the advantages are many: the B.M.R., which tends to fall when calories are reduced, does not do so so much as on a diet normal but for its caloric content; it has a very high satiety value, perhaps because it protects against reactive hypoglycaemia; ketosis (as the authors imply in one paragraph, contradicting themselves later on the same page) does not develop; and it can be continued for life without detriment to happiness or health.

But there is so much good in this book that such matters of disagreement should not be given too much importance. Is it for the first time in a book on the subject of obesity that the fact is stressed that the adipose tissue is an active organ under the control of the autonomic nervous system, storing or losing fat according to whether the nerve supply is interrupted or stimulated? Certainly the importance of close supervision, of the inculcation of permanent proper eating habits, of a slow but steady loss, of the use of the eyes rather than the tables in deciding the target, have never been more sanely expressed.

RAYMOND GREENE.

CLINICAL PERIMETRY

The Visual Fields: A Textbook and Atlas of Clinical Perimetry. By David O. Harrington, A.B., M.D., F.A.C.S. (Pp. 327; illustrated. £6.) London: Henry Kimpton. 1957.

Of recent years the science of clinical perimetry has been enriched by two good books in English literature—the new edition of Traquair's classical volume (the first to set the standard for all subsequent writing) by George Scott written primarily from the ophthalmological point of view, and that of Brodie Hughes written primarily from the neurological point of view. From America has appeared a companion volume by David Harrington, of California, an acknowledged authority on this subject, to which he has made several original contributions. Knowing the author, one would expect the book to be good; in view of his long and close association with neurology and neurosurgery and his ophthalmological pupillage under Traquair, one would expect it to be complete; and one is not disappointed, for the book is excellent.

The first part—on the technique of the examination of the visual fields—is unusually interesting because of the lucid presentation of new methods. Simple and often indispensable methods are not forgotten, such as confrontation and the use of the standard perimeter and screen; in addition, a clear and balanced exposition is given of such special techniques as angioscotometry, the testing of the fields with ultra-violet light and fluorescent test-objects (extremely valuable, since by this method all extraneous stimuli can be eliminated), the method of simultaneous double stimulation for eliciting the extinction phenomenon, flicker fusion fields, the multiple-pattern method (a technique introduced by the author), and so on. The following sections on the anatomy and vascularization of the visual pathways are equally good, and are particularly characterized by the clarity and originality of the illustrations.

The main part of the book details the abnormalities found in the visual fields in ocular and central nervous disease and psychogenic disturbances, each condition being clearly illustrated with descriptions of clinical cases. It is a manual which will certainly be of value to every ophthalmologist and neurologist, and is undoubtedly an asset to the literature. Every luxury—in typography and pictorial artistry—has been expended on the publication—a circumstance which no doubt accounts for its somewhat high cost.

STEWART DUKE-ELDER.

THE GERMAN POLICLINIC

Die Würzburger Medizinische Universitäts-Poliklinik, 1807–1957. By Hans Franke, Joachim Schröder, and Edith Schröder. (Pp. 123+xi; illustrated. DM. 15.) Stuttgart: Georg Thieme Verlag. 1957.

This volume, published to commemorate the 150th annisary of the Würzburger Medizinische Universitäts-Poliklinik, is mainly a historical survey of its development. The policlinic arose from the need to introduce the German medical student to clinical medicine at the bedside rather than to teach him purely systematic medicine—a conception which had apparently developed in Paris, Leyden, and even Vienna during the seventeenth century but did not penetrate to Germany until the Julius Hospital, forerunner of the policlinic, was established in Würzburg in 1769. Pioneers, including the celebrated Virchow, fought to bring such a clinic within the jurisdiction of the Faculty of Medicine of the University. It was not, however, until the beginning of the present century that friction between municipality and university was finally resolved. The policlinic, broadly translated as an out-patient department, was in many ways in advance of hospital practice. Its approach was human rather than academic, and the doctors who staffed it encountered an endless variety of minor and major maladies, involving almost every system. Moreover, such an out-patient department dealt with preventive no less than curative medicine, and had a fund of clinical material. Epidemiology and social medicine have long been studied within its precincts, while it has always been a fruitful field for the study of geriatrics. To-day the policlinic, like the out-patient departments of the modern teaching hospital, has become subdivided into almost every specialized department, although its chief concern appears to be their integration with general medicine. Modern diagnostic measures—such as, for example, bronchography, bronchoscopy, and oesophagoscopy in intrathoracic disease, and most other endoscopic procedures—have encouraged the provision of a small in-patient unit where the turnover of patients, by reason of the short stay, is very much more rapid than in hospital.

Since the war the Würzburger Poliklinik has been well equipped and housed in a magnificent new building, which includes clinical lecture theatre, out-patient clinics, comprehensive clinical and research laboratories, *x*-ray diagnostic and therapy departments, cardiographic department, a library, and an administrative and records department, many of which are handsomely illustrated and described in this volume. Although its purpose has changed somewhat now that clinical medicine is widely recognized as a basis of medical teaching, it still has a very useful part to play. It provides a valuable bridge between hospital instruction and general practice, comparable to some extent with the British pre-registration year. The policlinic is under the combined authority of the municipality, additionally financed by private enterprise, and the Faculty of Medicine of the University. It appears to be an important factor in German medicine, and this painstaking and factual volume offers a number of ideas that might possibly be of interest to the administrators of medicine in this country.

PHILIP ELLMAN.

INTRODUCTION TO MENTAL HEALTH

A Mental Health Handbook. By Ian Skottowe, M.D., M.R.C.P., D.P.M. (Pp. 196+vii. 21s.) London: Edward Arnold (Publishers) Ltd. 1957.

This introduction to mental health and the relevant social services is written mainly for health visitors, social workers, and others in the public-health services who have the function of furthering social action towards the prevention and treatment of mental ill-health. Its scope is therefore wide rather than deep: the varieties of mental ill-health are described in 32 pages, psychological development and deterioration from the womb to the tomb in 34. These form succinct introductions to these subjects for those for whom the book is intended. The author also outlines the present mental health services and the ways in which authorities in various localities might set up or expand an efficient mental health service. The book is governed throughout by common sense. On the subject of health education, for example, the author says that this should primarily be health education and not an incitement to illness-consciousness and hypochondriasis. He points out the limitations of psychiatry: that, for example, one can rarely cause a man who is irritated by every action of his wife to feel affectionate towards her, or cause a mother to love her child if at heart she rejects him. He criticizes the concept of flight into illness when applied to the "psychological chaos of advanced schizophrenia" or "the self-condemnatory agony of profound melancholia."

This book can be read with value by those for whom it is primarily intended—social workers and the like—and medical students will also find it of value as an introduction to psychiatry.

A. W. BEARD.

Studies on Fertility, Volume VIII of the proceedings of the Society for the Study of Fertility, consists principally of papers read at the Society's London conference in 1956, and includes the results of both clinical and experimental investigations. It is published by Blackwell Scientific Publications Ltd., Oxford (pp. 138+x. 25s.).

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IMMUNOLOGY AND CANCER RESEARCH

In recent years there has been a considerable revival in the serological investigation of malignant disease. H. N. Green has published a series of papers advocating an immunological theory of cancer postulating antigenic loss as an essential stage in the development of malignancy. On the other hand there is increasing evidence of novel antigenic properties in malignant tumours.

For various reasons malignant cells may be regarded as defective. The most direct evidence perhaps comes from carcinogenesis in the liver of rats by dyes such as dimethylaminoazobenzene (butter yellow), a subject well reviewed by J. A. Miller and E. C. Miller.[1] Part of the dye is bound to proteins in the liver parenchyma; the amount of dye bound reaches its maximum at about a month but thereafter declines, and has fallen to about 50% of the maximum by four months. The binding power of liver falls when tumours are likely to occur, and the tumours themselves cannot bind the dye. For this and other reasons the Millers think that malignancy is causally associated with the loss of this protein fraction, which must play some vital part in the regulation of growth. E. Weiler,[2] using fluorescent antibodies, showed the loss of an antigenic fraction during carcinogenesis by this dye. He believed the antigen to be organ specific and considered that some new antigen might be present in the tumours. He obtained a similar result with renal tumours induced by oestrogen in hamsters.[3 4]

A different approach is seen in the genetic studies initiated by Little, Strong, Bittner, and Cloudman and put into antigenic terms by P. A. Gorer and co-workers. The most recent review of this work is by Gorer.[5] If tumours arising in pure strains of mice are studied genetically they behave as if iso-antigens are progressively lost during transplantation, though Gorer contends that the picture is complicated by the fact that tumours can grow in the presence of iso-antigenic differences. He first deduced this by reference to earlier work on a phenomenon known as concomitant immunity, but now he and his colleagues have put the matter beyond doubt.[6 7] This property may be of clinical interest. While some loss of iso-antigens undoubtedly can occur,[8–10] Gorer[5 11] seems to think that quantitative changes are commoner than actual loss. It is not clear how far these changes are associated with growth rate or malignancy in autochthonous tumours.

Green has not presented direct evidence of antigenic loss, and some of his data seem to point in the contrary direction. Thus he considers that the anaemia of advanced malignancy may be explained by the production of antibodies by the tumours against the host. That this may occur occasionally is shown by the dramatic case reported by A. Lacassagne and M. Bessis.[12] However, Green and his colleagues[13] seem to think that it is of general occurrence once the tumour mass is large enough. If the terminal anaemia of malignant disease is really an example of auto-immunization, it is difficult to believe that the antibodies are formed by defective mammary epithelial cells and the like. A more probable explanation would seem to be that a large amount of antigenic material was being released by the tumour, adsorbed on the erythrocytes, and the antibodies produced by the patient. But it is not yet certain that the terminal anaemia is necessarily an example of auto-immunization.

It may well be true that neoplasia occurs only if some cellular receptor is lost, but it does not seem possible to account for malignancy in terms of the loss of a single receptor. The loss of a single receptor might account for the formation of such a lesion as Bowen's disease—a precancerous dermatosis—but further modifications must occur to account for invasiveness, lack of response to hormonal inhibition, and so on. It is to be hoped that immunological techniques will help to identify such components as may be lost, for with the exception of Weiler's work they have not done so yet.

[1] Miller, J. A., and Miller, E. C., *Advanc. Cancer Res.*, 1953, **1**, 340.
[2] Weiler, E., *Z. Naturf.*, 1952, **7b**, 327.
[3] —— *Brit. J. Cancer*, 1956, **10**, 553.
[4] —— ibid., 1956, **10**, 560.
[5] Gorer, P. A., *Advanc. Cancer Res.*, 1956, **4**, 149.
[6] —— *J. Path. Bact.*, 1948, **47**, 231.
[7] Amos, D. B., Gorer, P. A., and Mikulska, Z. B., *Brit. J. Cancer*, 1955, **9**, 209.
[8] Hoecker, G. S., and Hauschka, T. S., *Transplant. Bull.*, 1956, **3**, 134.
[9] Amos, D. B., *Ann. N.Y. Acad. Sci.*, 1956, **63**, 706.
[10] Klein, E., Klein, G., and Revesz, L., *J. nat. Cancer Inst.*, 1957, **19**, 95.
[11] Gorer, P. A., *Brit. J. Cancer*, 1948, **2**, 103.
[12] Lacassagne, A., and Bessis, M., *Ciba Foundation Symposium on Leukaemia Research*, 1954, 134.
[13] Green, H. N., Wakefield, J., and Littlewood, G., *Brit. med. J.*, 1957, **2**, 779.
[14] Hauschka, T. S., *Cancer Res.*, 1952, **12**, 615.
[15] Snell, G. D., in *Physiopathology of Cancer*, 1953, edited by Homburger, F., and Fishman, W. K., New York, 338.
[16] Zilber, L. A., *J. nat. Cancer Res.*, 1957, **18**, 341.
[17] Gorer, P. A., and Amos, D. B., *Cancer Res.*, 1956, **16**, 338.
[18] Amos, D. B., and Day, E. D., *Ann. N.Y. Acad. Sci.*, 1957, **64**, 851.
[19] Lewis, M. R., and Aptekman, P. M., *Cancer*, 1952, **5**, 411.
[20] Foley, E. J., *Cancer Res.*, 1953, **13**, 578.
[21] Prehn, R. T., and Main, J. M., *J. nat. Cancer Inst.*, 1957, **18**, 769.

Most immunologists have concentrated on attempts to detect novel antigenic components in neoplastic cells. Excellent reviews of earlier work have been made by T. S. Hauschka[14] and G. D. Snell,[15] while extensive studies by L. A. Zilber and his school in Moscow have recently been reviewed in English.[16] These Russian workers have studied many tumours in man and animals; only a small amount of work has been done with inbred strains. Zilber thinks that virus tumours have a new constituent in addition to the virus. This is an interesting conception, for it is well known that the virus tumours such as the Shope papilloma and even the Rous sarcoma may regress, which is consistent with the idea that a new antigen has been formed. While all accept as valid the finding of viral antigens in certain tumours, geneticists have long had misgivings about the validity of claims made for other novel antigenic components. This is quite justifiable with regard to some of the results obtained with long-transplanted tumours. An antigenic component in the Walker rat carcinoma may have been common in the colony of rats in which the tumour arose, but it might easily be absent in the colony in which it is now maintained. Similar reservations must be felt about work on human tumours. Suppose an antigen is found in a hepatoma from patient A that is absent in the healthy liver of patient B, how can we be sure that the difference is not due to different genetically determined iso-antigens? With skin tumours we might use normal and malignant tissue from the same individual, but in many other cases an adequate control is impossible. However, work with inbred strains of mice has recently shown that new antigenic components of tumours do occur.

Gorer and D. B. Amos[17] worked with a leukaemia (E.L.4) arising in the C57BL strain of mice, which it invariably kills in about 21 days. In foreign strains the neoplasm will produce a subcutaneous tumour about 1 cm. in diameter that then regresses. Hyperimmune sera from resistant strains will inhibit this temporary growth if injected before or shortly after the cells. This is of interest because it is the first time that passive immunity to any type of transplant has been successful with serum. These workers were then surprised to find that such sera would give protection in the C57BL strain even when administered as long as a week before the malignant cells. This protection cannot be due to iso-antibodies, and the authors called the antibody anti-X. They considered the possibility that the C57BL strain might have had X as an iso-antigen when E.L.4 arose but it has now been lost by genetic mutation. This does not seem to be so, and Gorer[5] has recorded the discovery of the same or a very similar antigen in a new C57BL leukosis. Amos and E. D. Day[18] found X components in three leukaemias arising in other strains all antigenically different from one another. The nature of the X components remains to be determined; they may be viruses or viral products.

When tumours that arise in pure strains are made to grow in hosts that are known to differ antigenically from the strain of origin, there is no difficulty in showing that antigenic differences are being overridden. It is possible to immunize the animals with normal tissues from the strain of origin, as was done by Amos and his colleagues.[7] To see if this is occurring within a pure strain, the only possible method is to remove the tumour. This may be done by various means: M. R. Lewis and P. M. Aptekman[19] cut off the circulation of the tumour by gradually tightening a ligature round its base. The results of their experiments are ambiguous, but the method gave decisive results in the hands of E. J. Foley[20] and R. T. Prehn and J. M. Main.[21] Foley used the C3H strain of mice, and his first experiments were done with mammary carcinomata to which the strain are very susceptible. No immunity to the carcinomata was induced within the strain by this method, but definite immunity was obtained against sarcoma induced by methyl cholanthrene. Within a given pure strain no single "cancer" antigen is found to be formed, although such antigens as are formed seem to be related. The pertinent antigen(s) can be lost during transplantation. Gorer[5] and Prehn and Main[21] offer very tentative suggestions on the apparent differences between the antigenic properties of spontaneous and induced neoplasms. Doubtless all would agree that the data are too meagre yet for interpretation. The important point is that a potentially effective antigenic difference between an autochthonous neoplasm and its host has now been detected. This would indicate that the ability of transplanted tumours to override antigenic differences may be of more than academic interest and this may be of importance in future approaches to therapy.

To summarize, we may say that immunology cannot yet tell us the essential differences between normal and neoplastic cells. Cellular deficiencies may be of importance, but the techniques of immunology have done very little to demonstrate them. Immunogenetic studies have shown that neoplasms can override potentially effective antigenic differences. Some tumours possess antigens potentially capable of inducing resistance in individuals genetically identical with the animals in which tumours have been chemically induced. Any general immunological theory of cancer is evidently premature.

NEUROTOXIC EFFECTS OF ISONIAZID

Isoniazid has been used for the treatment of tuberculosis for nearly six years and is generally believed to be the most effective drug available. Fortunately its efficacy is paralleled by a remarkable lack of toxicity in ordinary dosage. Nevertheless evidence is accumulating that isoniazid has certain serious toxic effects which tend to be more severe in adults than in children and may particularly affect alcoholics, especially if the dosage exceeds 5 mg. per kg. of body weight daily. These toxic effects are largely preventable, but, as a recent report[1] from the World Health Organization has stressed, it is important that they should be recognized as soon as they appear. In 1953 the Committee of Therapy of the American Trudeau Society[2] estimated that toxic reactions to isoniazid occurred in about 5% of patients and that in 1% the reaction was serious enough to contraindicate treatment. The nervous system was most commonly affected. Of the neurological complications, peripheral neuritis, convulsions, optic atrophy with blindness, and major psychoses are the most important. Peripheral neuritis is the commonest and was noted early by E. H. Robitzek and I. J. Selikoff[3] in the U.S.A. as well as by German authors.[4 5] In one series of some 500 patients with pulmonary tuberculosis treated with 4–8 mg./kg. doses of isoniazid, 8 developed peripheral neuritis,[6] but in another series of 17 given 20 mg./kg. doses daily 6 developed peripheral neuritis.[7] J. P. Biehl and R. W. Vilter[8] showed that the incidence was 2% on a dose of 3–5 mg./kg., but rose to 4% when doses of 6–24 mg./kg. were given, and the neuritis appeared much sooner on the higher dose. S. Katz and his colleagues[9] found a similar relationship between onset of neuritis and size of dose. The incidence of neuritis was reported to be particularly high in patients on second or subsequent courses of isoniazid.[10]

Biehl and H. J. Nimitz[10] found that isoniazid increased the number of fits in epileptics: large single doses given by mouth[11 12] or intramuscularly often caused convulsions,[13] and an epileptic patient who was having isoniazid by mouth remained in coma for three days after a fit.[14] Another patient attempted to commit suicide by taking between 3 and 10 g. of isoniazid, which led to a series of fourteen convulsions.[15] Optic atrophy with or without blindness has been noted in patients given isoniazid for the treatment of pulmonary tuberculosis.[16–20] In two cases discontinuation of isoniazid reversed the process.[17 20] One patient died,[18] and at necropsy demyelination of the optic tracts and softening of the grey matter of the spinal cord were found. As optic atrophy and blindness are well-recognized sequelae of tuberculous meningitis, it would be wrong to attribute these complications solely to isoniazid therapy, but G. Janssen and W. Böke[21] found that the incidence of optic neuritis, optic atrophy, and blindness had increased from 13 out of 94 cases treated in a period before isoniazid was introduced to 28 of 45 in patients treated with intrathecal isoniazid. In most cases it is not necessary to give isoniazid intrathecally,[22] and the high incidence of visual complications associated with this method of administration should serve as a warning against its routine use.

Psychosis due to isoniazid is also well recognized: it was reported in 4 of 173 patients treated in the first Medical Research Council's trial,[23] and other reports have since appeared.[14 15 24–31] S. L. O. Jackson[32] has recently described five cases in this *Journal*. Several authors have observed that withdrawal of isoniazid usually but not invariably led to a disappearance of the symptoms.

Animal studies have also shown that isoniazid has neurotoxic properties.[33 34] Rats developed degeneration of peripheral nerves in the legs after 7 to 8 months on 200–250 mg./kg. of isoniazid daily, but focal degeneration of the medullary sheaths was already present after only 15 days.[35] Biehl and Vilter[8] noted that the peripheral neuritis

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[1] *Wld Hlth Org. techn. Rep. Ser.*, No. 141, "Chemotherapy and Chemoprophylaxis in Tuberculosis Control," 1957, Geneva.
[2] *Amer. Rev. Tuberc.*, 1953, **60**, 302.
[3] Robitzek, E. H., and Selikoff, I. J., ibid., 1952, **65**, 402.
[4] Heilmeyer, L., Schaich, W., Buchegger, G., Kilchling, H., Schmidt, F., and Walter, A. M., *Münch. med. Wschr.*, 1952, **94**, 1303.
[5] Klee, P., *Dtsch. med. Wschr.*, 1952, **77**, 578.
[6] Oestreicher, R., Dressler, S. H., and Middlebrook, G., *Amer. Rev. Tuberc.*, 1954, **70**, 504.
[7] Hughes, H. B., Biehl, J. P., Jones, A. P., and Schmidt, L. H., ibid., 1954, **70**, 266.
[8] Biehl, J. P., and Vilter, R. W., *J. Amer. med. Ass.*, 1954, **156**, 1549.
[9] Katz, S., Gruver, R., Smith, B., and McCormick, G., *Dis. Chest*, 1954, **26**, 264.
[10] Biehl, J. P., and Nimitz, H. J., *Amer. Rev. Tuberc.*, 1954, **70**, 430.
[11] Grimminger, A., *Beitr. Klin. Tuberk.*, 1953, **110**, 387.
[12] Aiazzi Mancini, M., *Minerva med. (Torino)*, 1954, **1**, 529.
[13] Reilly, R. H., Killam, K. F., Jenney, E. H., Marshall, W. H., Tausig, T., Apter, N. S., and Pfeiffer, C. C., *J. Amer. med. Ass.*, 1953, **152**, 1317.
[14] Vysniauskas, C., and Brueckner, H. H., *Amer. Rev. Tuberc.*, 1954, **69**, 759.
[15] Barbořík, M., and Wiedermann, M., *Vnitřní Lék.*, 1955, **1**, 760.
[16] Sutton, P. H., and Beattie, P. H., *Lancet*, 1955, **1**, 650.
[17] Keeping, J. A., and Searle, C. W. A., ibid., 1955, **2**, 278.
[18] Dixon, G. J., Roberts, G. B. S., and Tyrrell, W. F., *Scot. med. J.*, 1956, **1**, 350.
[19] Carlson, H. B., Anthony, E. M., Russell, W. F., and Middlebrook, G., *New Engl. J. Med.*, 1956, **255**, 118.
[20] Kass, I., Mandel, W., Cohen, H., and Dressler, S. H., *J. Amer. med. Ass.*, 1957, **164**, 174.
[21] Janssen, G., and Böke, W., *Klin. Wschr.*, 1955, **33**, 477.
[22] Lorber, J., *Brit. med. J.*, 1956, **1**, 1009.
[23] Medical Research Council Report, ibid., 1952, **2**, 735.
[24] McConnell, R. B., and Cheetham, H. D., *Lancet*, 1952, **2**, 959.
[25] Hunter, R. A., ibid., 1952, **2**, 960.
[26] Zabad, M., ibid., 1953, **1**, 295.
[27] Conrad, K., and Scheib, E., *Dtsch. med. Wschr.*, 1953, **78**, 604.
[28] Kiersch, T. A., *U.S. armed Forces med. J.*, 1954, **5**, 1353.
[29] Wiedorn, W. S., and Ervin, F., *A.M.A. Arch. Neurol. Psychiat.*, 1954, **72**, 321.
[30] Hayes, J. W., *Amer. Rev. Tuberc.*, 1954, **69**, 845.
[31] Wood, M. M., *Brit. J. Tuberc.*, 1955, **49**, 20.
[32] Jackson, S. L. O., *Brit. med. J.*, 1957, **2**, 743.
[33] Ungar, J., Tomich, E. G., Parkin, K. R., and Muggleton, P. W., *Lancet*, 1954, **2**, 220.
[34] Grunberg, E., and Biencowe, W., *Amer. Rev. Tuberc.*, 1955, **71**, 898.
[35] Zbinden, G., and Studer, A., *Z. Tuberk.*, 1955, **107**, 97.
[36] Bessey, O. A., Adam, D. J. D., and Hansen, A. E., *Pediatrics*, 1957, **20**, 33.
[37] Wasz-Höckert, O., McCune, R. M., and Tompsett, R., *Amer. Rev. Tuberc.*, 1956, **74**, 471.
[38] Jones, W. A., and Jones, G. P., *Lancet*, 1953, **1**, 1073.

induced by isoniazid was similar to that induced by the vitamin B_6 (pyridoxine) antagonist, desoxypyridoxine, and they therefore studied pyridoxine metabolism in tuberculous patients receiving isoniazid in various doses. They found a striking increase in the urinary excretion of pyridoxine and pyridoxic acid (an inactive metabolite of pyridoxine), an increase proportionate to the dose of isoniazid. The abnormal excretion disappeared on discontinuing the drug. Pyridoxine is essential for the normal metabolism of tryptophan, and in its absence xanthurenic acid appears in the urine in large quantities, as it did in patients on isoniazid. The administration of pyridoxine to these patients put a stop to the excretion of xanthurenic acid, and subsequently Biehl and Vilter treated 20 patients with 20 mg./kg. of isoniazid together with 50–450 mg./kg. of pyridoxine daily for at least ten weeks and none developed neuritis. Other workers[6 19 20] have found pyridoxine in doses of the order of 50 mg. daily to be effective in the treatment of peripheral neuritis, psychosis, and the other neurotoxic manifestations of isoniazid, just as O. A. Bessey *et al.*[36] showed pyridoxine would control infantile convulsions due to its deficiency in the diet. It seems, therefore, that a case can be made out for the routine administration of pyridoxine to patients receiving isoniazid, especially when large doses are used and during the treatment of tuberculous meningitis, because in such cases all the toxic complications can be mistakenly attributed to the disease itself. Fortunately, the addition of pyridoxine does not diminish the chemotherapeutic properties of isoniazid.[33 34 37] There is some evidence that pyridoxine is not the only member of the vitamin-B group which may become deficient during isoniazid therapy. Cases have been described in which typical pellagra developed and which responded to nicotinamide,[24 31 38] and some cases of psychosis also responded to nicotinamide but not to other members of the vitamin-B group. Jackson[32] found better response when a vitamin-B complex was given parenterally, and suggests that this is the treatment of choice in those who have already developed neurological side-effects.

DETECTING GLAUCOMA EARLY

The "tactus eruditus" is part of ocular mythology, and it is possibly a mean kind of iconoclasm to doubt the ophthalmic mandarins of our student days. Nevertheless, whenever the belief that the ocular tension can be accurately gauged by palpation through the lids has been put to the test by controlled investigation, the procedure has been found unreliable even in the hands of the experienced.[1 2] H. A. Schiøtz,[3] of Oslo, devoted the greater part of his life to the perfection of the tonometer, which works on the simple principle that an eye with low tension dimples more easily than one with high intraocular pressure. When it is used for comparative measurement, as in comparing the two eyes of the same individual at the same time, it can detect very slight differences of pressure; while in following the variations of tension in the same eye at different times it provides a series of observations which is free from subjective interpretations and cannot be obtained by any other method. The only serious inaccuracy, now that calibration has been undertaken by the W. H. Ross Foundation,[4 5] is due to abnormal rigidity of the sclera, but this complication can be readily recognized by multiple readings.[6–8] The problems which remain with us to-day are how this instrument should be used and who should use it. At a recent meeting of the Ophthalmological Society of the United Kingdom a paper on this subject was read by H. Reed.[9] He and his colleague, J. E. L. Bendor-Samuel, started an investigation expecting to prove routine tonometry to be of doubtful value. To their surprise the opposite was found. In two thousand consecutive ophthalmic examinations in patients over the age of 40, 58, or 2.9%, were proved to have glaucoma. Of these 58, 30 appeared clinically normal, and their disease would not have been recognized but for this method of testing. Other surveys of this kind have been made,[10–12] and the percentage of cases of glaucoma which would have been similarly missed ranged between 1.8 and 2.6. These results are of great clinical importance, because it is well known that much can be done to stay the progress of glaucoma if it is diagnosed early in its course, whereas in the later stages of the disease the deterioration in the field of vision is inexorable.[13] Of the one hundred thousand blind people in Great Britain some 15% have lost their vision because of glaucoma, and, of these, two-thirds have fully completed all possible treatment.[14] To reduce the incidence of blindness due to glaucoma it would seem necessary not only to make a diagnosis but to make it at the right time, and it is impossible, with this in mind, to disregard the results of routine tonometry. So far the tonometer has been used exclusively by ophthalmic surgeons, but C. Berens and C. P. Tolman,[15 16] stimulated by the estimation that about one million adults in the United States suffer from glaucoma and

[1] McDonald, J. E., and Caygill, W. M., *J. Amer. med. Ass.*, 1957, **165**, 1131.
[2] Mueller, H. K., *Arch. Augenheilk.*, 1930, **102**, 668.
[3] Schiøtz, H. A., *Acta ophthal. (Kbh.)*, 1926, **4**, 1.
[4] Jackson, C. R. S., *Proc. roy. Soc. Med.*, 1957, **50**, 674.
[5] —— *Brit. J. Ophthal.*, 1955, **39**, 368.
[6] Friedenwald, J. S., *Amer. J. Ophthal.*, 1937, **20**, 985.
[7] —— ibid., 1948, **31**, 935.
[8] —— *Trans. Amer. Acad. Ophthal. Otolaryng.*, 1949, 261.
[9] Reed, H., and Bendor-Samuel, J. E. L., *Trans. ophthal. Soc. U.K.*, 1957, **77**, 379.
[10] Phelps, G. D., *J. Iowa St. med. Soc.*, 1949, **39**, 519.
[11] Bendor-Samuel, J. E. L., and Reed, H., *Winnipeg Clin. Quart.*, 1956, **9**, 144.
[12] Hildreth, H. R., and Becker, B., *Amer. J. Ophthal.*, 1957, **43**, 21.
[13] Kronfeld, P. C., and McGarry, H. I., *J. Amer. med. Ass.*, 1948, **138**, 957.
[14] Sorsby, A., *Blindness in England 1951–1954*, 1956, H.M.S.O., London.
[15] Berens, C., and Tolman, C. P., *J. Amer. med. Ass.*, 1950, **142**, 1360.
[16] —— *Acta XVI Concilium Ophthal.*, 1950, **2**, 1499.

do not know it, have devised a simple, inexpensive tonometer and have advocated its use by general practitioners in mass health surveys. The need to alleviate glaucomatous blindness in Great Britain is undoubted, and ophthalmic medical practitioners might profitably consider adding tonometry to their routine tests when examining patients over the age of 40. Ophthalmic outpatient officers in hospital who are not already overwhelmed by routine work might do the same.

ANTICHOLINE DRUGS

Among the innumerable drugs offered to the doctor by the pharmaceutical manufacturers, a large group are intended to relax spasm and reduce motility in smooth muscle as effectively as atropine, without producing its many side-effects. It is perhaps because they are all only partially successful that they are so numerous. They are often called anticholinergic. Cholinergic, however, is an adjective which can be applied only to a nerve, since it means "works by liberating acetylcholine," and therefore it is incorrect to speak of anticholinergic drugs. They are better described as anticholine substances in accord with the use of the term antihistamine substances. The ingenuity of chemists in this field has had little success, since in the United States the preparation which is by far the most widely prescribed is "donnatal," a mixture of the naturally occurring substances atropine, hyoscine, and hyoscyamine. A long way second comes propantheline bromide, which is a synthetic compound containing quaternary nitrogen, and which is widely used in Britain. Substances containing quaternary nitrogen usually have a ganglion-blocking action in addition to their effect at the postganglionic nerve endings; they are not well absorbed from the intestine and thus they are relatively free from side-effects. Both methantheline and propantheline have been strongly recommended for the control of spasm and hypermotility of the gastro-intestinal tract. The quaternary forms of atropine and hyoscine, the methylnitrates, both have a good reputation for the treatment of pyloric stenosis in babies.

In *New and Nonofficial Remedies*, up to 1957, there were fourteen drugs described as being effective in relieving the symptoms of peptic ulcer, of which the first five are diphenamil, homatropine methylbromide, methantheline, hyoscine methylbromide, and hyoscine methylnitrate. There is no evidence which is the best, and it is probable that most clinicians will prefer to become acquainted with the use of one or two. Methantheline is said to be more effective for duodenal ulcer. The results obtained with all the members of this group may be varied by their mode of administration. When a quick action is needed they should be given on an empty stomach or by injection. When a mild sustained effect is wanted they should be given either with meals or after them. There is no doubt that these drugs are useful for patients who have ulcers, because they diminish the secretion of acid and lessen motility, but they do not promote healing. When an ulcer obstructs the pylorus and interferes with the emptying of the stomach these drugs are contra-indicated, as they are when there is a peptic ulcer which bleeds. They should not be used in cardiospasm, which is a disorder of the cholinergic innervation of the oesophagus, leading to impaired propulsion and to failure of relaxation at the lower end.

The usual side-effects of the anticholine drugs are dryness of the mouth and constipation, and there may be tachycardia, so that these substances should not be given to those with angina. The inhibitory action on smooth muscle may cause urinary retention. Large doses may lead to paralysis of the sphincter of the pupil and so to raised intraocular pressure. Some observers think that by relieving pain these drugs may mask the warning symptoms preceding perforation of an ulcer and preceding haemorrhage.

DERMATITIS HERPETIFORMIS AND HERPES GESTATIONIS

Skin diseases peculiar to pregnancy merit particular attention for the light they may throw upon the aetiology of disease in general. B. Russell and N. A. Thorne[1] have lately reviewed the uncommon affection herpes gestationis. In their experience at the London Hospital it occurred once in every 3,000 to 4,000 deliveries, and a similar incidence was found by G. M. Crawford and R. W. Leeper[2] in Boston.

Herpes gestationis is characterized by pruritus and a polymorphic, vesico-bullous, erythematous eruption arising commonly in the second trimester. It clears spontaneously after confinement and recurs with subsequent pregnancies. The disease has many features in common with dermatitis herpetiformis, but it figured in medical literature long before Tilbury Fox[3] and L. A. Duhring[4] described the latter as a distinct clinical entity. Many believe that they are the same reaction and differ only in that the adequate stimulus in the one case is limited to the state of pregnancy. Increased levels of gonadotrophins, probably of pituitary origin, are found in blood and urine in herpes gestationis.

Herpes gestationis is not regularly controlled by such measures as arsenic, sulphapyridine, and dapsone as is dermatitis herpetiformis. The most effective treatment is steroid therapy, which Russell and Thorne regard as safe provided it is restricted to the second and early part of the third trimesters. It is interesting that dermatitis herpetiformis as it appears in children is similarly resistant to routine therapy, though it will sometimes respond to calciferol in moderately large doses. The disease in children usually clears before puberty. In the elderly the eruption commonly described as pemphigoid, and confused until recent years with pemphigus vulgaris, is regarded by many as dermatitis herpetiformis modified by old age. It is similarly resistant to arsenic,

[1] Russell, B., and Thorne, N. A., *Brit. J. Derm.*, 1957, **69**, 339.
[2] Crawford, G. M., and Leeper, R. W., *Arch. Derm. Syph. (Chicago)*, 1950, **61**, 753.
[3] Fox, T., *Arch. Derm. Philadelphia*, 1880, **6**, 16.
[4] Duhring, L. A., *J. Amer. med. Ass.*, 1884, **3**, 225.

sulphapyridine, and dapsone in most cases, but readily controlled by steroid therapy in moderate dosage.

Apart from their similar clinical features, all these disorders carry a good prognosis. But occasional variations from the general pattern of behaviour are observed. Thus dermatitis herpetiformis in childhood may rarely carry through to adult life and not clear at puberty. The ordinary Duhring type of dermatitis herpetiformis may continue from adult life into old age without change to the pemphigoid pattern. It has also been observed to continue through pregnancy without material change and without remission after confinement. It is perhaps no more than a reminder that these are all individual patterns of reaction to a variety of stimuli and are not clearly defined diseases of specific aetiology. Until more is known of the biochemical peculiarities of the skin, much must remain obscure.

THE NEW ESTIMATES

In an article in the *Supplement* this week a correspondent analyses the trend in Health Service expenditure during the years it has been in operation. Perhaps the main impression produced by the survey is one of steady expansion along the lines that, whether by accident or design, were laid down ten years ago. So much has been heard, from time to time, of the vast rise in the Service's money cost, particularly of the cost of the hospitals and of prescriptions, that the public tends to think that these branches of the Health Service have been obtaining more than their share of the funds available. It may be that the demand for a bottle of medicine is unhealthy and that there is too much emphasis on hospital treatment at the expense of family doctoring and the preventive services of local authorities. But the pattern has altered very little over the last ten years, and seems likely to continue unless there is some deliberate act of policy designed to upset it.

Year by year, however, the Chancellor of the Exchequer has to decide the question, How shall the money needed for the Service be raised ? Can he, when trying to reduce taxation—or at least prevent it from rising—allow the full extra cost to fall on the taxpayer ? The analysis given by our correspondent shows what devices have been tried over the past few years. Charges to patients yield eight to nine times more now than they did in 1949–50, when they were restricted to payments for private and amenity beds in hospital. But last year and in the financial year just begun the Government has switched some of the cost on to the Health Service portion of the weekly national insurance contribution. The effect has been to reduce the amount to be raised by taxes in 1958–9 to nearly £531m., compared with £545m. in the year just ended.

On the expenditure side, the estimates show the combined effects of the increases in pay announced in 1957–8 and the increase in numbers employed. But there is also a welcome increase of nearly £3m. in advances to hospital boards for their capital schemes. A list of these schemes, which include about a dozen entirely new hospitals, is given in an appendix to this year's estimates. There will be general relief that Britain is at last undertaking some new hospital building. But it has to be faced that when eventually they are finished they will have to be staffed and equipped and will therefore produce an unknown addition to the hospital service's maintenance expenditure.

AREA MORTALITY

The probability of dying from a certain cause often bears some relation to the place where a person dies. Deaths from bronchitis, for instance, are more prevalent in the north than in the south of England, and the probability of dying from it is twice as high in the north-western region as in the south-western. By contrast the probability of dying from lung cancer is one and a half times as high in London and the south-east as it is in the north midland region. The Registrar-General's latest analysis[1] of area mortality rates in England and Wales, from which these figures are taken, appeared this week and some of its findings are illustrated at p. 884 of the *Journal*.

The value of such analyses is that they may draw attention to features in the environment that are damaging the inhabitants' health. Cancer of the stomach is shown to be much more prevalent in Wales than in England, for example, and for some time P. Stocks and other workers[2] have been investigating possible reasons for it. A striking inverse relationship is evident between cancer of the breast and cancer of the uterus. In the north breast cancer is low and uterine cancer high in frequency ; in the south the reverse is found. Deaths from suicide have much the same frequency in the various English regions, but notably lower in Wales, where the rate is only three-quarters of the rate in England. The effect of environment on health as measured by such death rates is sometimes obscured by other influences. Different diseases are apt to strike down rich and poor, or slate quarriers and market gardeners, or coal-miners and lawyers,[3] and it is only in certain places that riches may be won, slate quarried, turnips dug, and so on. The uneven distribution of economic classes and occupations may thus account for some of the differences in area mortality, but enough remain to point to the need for more studies in public health. We learn, for instance, that in 1950–3 deaths from peptic ulcer were uncommonly low in rural districts, deaths from hyperplasia of prostate high in Wales, from leukaemia one and half times as high in the southern region of England as in the northern, and from meningococcal infections twice as high in the northern region as in the southern. Life is not altogether what we make it, and no more is death, but statistics of this kind do help to extend man's control of the environment for the improvement of his health.

Professor Robert Platt was re-elected President of the Royal College of Physicians of London on March 31.

[1] *Registrar-General's Decennial Supplement, England and Wales, 1951, Area Mortality*, 1958, H.M.S.O.
[2] *Brit. med. J.*, 1957, **1**, 331.
[3] Ibid., 1958, **1**, 637.

AREA MORTALITY IN ENGLAND AND WALES

The maps below enable a comparison to be made of the frequency of certain common causes of death in the standard regions of England and Wales during the period 1950–3. The figures show, for each region, the actual numbers of deaths as a percentage of the "expected" number. This is the number that would have occurred there if the death rate had been the same as the rate for the whole country. The rates are standardized for age and sex. Thus the map for "All causes of death" shows that in the Northern Region male mortality was 107% of that for England and Wales as a whole, and female mortality 109%. The figures are taken from the *Registrar-General's Decennial Supplement, England and Wales, 1951, Area Mortality* published this week (H.M.S.O., 70s.).

The Registrar-General's standard regions are shown in the maps. The figures in bold type refer to deaths of **males** and in italic type to deaths of *females*, except in Fig. 9, where deaths of males and females are combined. In Fig. 6 male deaths do not appear.

The previous decennial report on area mortality was for the years 1921–30. Comparison of the present one with it shows some improvement of mortality ratios in the north of England. For all causes of death combined they were then 113 (males) and 115% (females) of the average for the country; in the new report they are 108 and 108. By contrast, Wales shows a slight deterioration: from 102 (males) and 107 (females) to 108 and 108 also.

FIG. 1.—All causes of death.

FIG. 2.—Arteriosclerosis and coronary disease.

FIG. 3.—Vascular lesions affecting central nervous system.

FIG. 4.—Cancer of stomach.

FIG. 5.—Cancer of trachea, lung, and bronchus.

FIG. 6.—Cancer of breast (females only) *above* names, cancer of uterus *below* names.

FIG. 7.—Bronchitis.

FIG. 8.—Respiratory tuberculosis.

FIG. 9.—Infant mortality *above* names, Stillbirths *below* names.

THE FEAR OF DEATH

On March 13 Dr. ELIOT SLATER lectured to the Euthanasia Society, following their annual meeting, on "The Biologist and the Fear of Death." In his lecture Dr. Slater discussed how a biological outlook might help a man to face his end more calmly.

A little while ago, said Dr. Slater, a friend had suffered a bereavement. His mother-in-law, an old lady of 76 who enjoyed only very feeble health, was taken suddenly ill with a stroke. She was paralysed down her right side and unable to speak. There seemed to have been some panic in the home, for, instead of putting her to bed when a doctor could not be obtained at once, first the hospital and then the ambulance service were called. The old lady was put in the ambulance and, sinking fast, was driven to a famous teaching hospital. By the time she was wheeled into the casualty ward she had breathed her last. But the young and efficient casualty officer was far from being dismayed. All the resuscitation services that the hospital could provide were mobilized, and for eighteen hours the patient's heart was kept beating and the elaborate and beautiful apparatus for artificial respiration did her breathing for her. Mercifully enough, this determined battle was fought in vain.

When asked later what had been the point of it all, the casualty officer gave a very significant reply. He admitted that, even if it had been possible to preserve the patient's life, only the shell of a human being, speechless, paralysed, and demented, would have remained. Yet, he maintained, it was not within his discretion to think of what the ultimate issue would be. He had one duty, and one duty only: to do all that lay within his powers to ward off death.

A Time to Allow Death

This, said Dr. Slater, was not quite the teaching he himself had enjoyed when a medical student. He had been taught, "Thou shalt not kill, but needst not strive officiously to keep alive." Nevertheless, the point of view expressed by the young doctor was one which in this age was probably beginning to gain ground; and, if this were so, then we must examine again the basic principles on which we faced the primary issues of life and death.

One person with whom Dr. Slater had discussed the case had warmly supported the casualty officer's view. Anything less, he had felt, would be liable to grave abuse. Who was the doctor to assume the responsibility of letting a patient die? Even if the most energetic treatment was only likely to secure a few more days of life, it should not be spared. If the duty of the medical man was to be assessed in that way, then logically the doctor must disturb the dying man to provide him with a few more hours. But, if the process was not pushed to its last absurd limits, then wherever else the line was drawn the doctor could not evade the responsibility of saying that now the time had come to let death take its course. This, surely, was one of a doctor's natural and inescapable responsibilities.

A busy general practitioner had taken yet another view. He had thought that an older and more experienced man would have probably refrained from doing all the casualty officer did; but that what was right for the older man was not necessarily right for the younger. Until one had learned the limits of one's craft, one should seek to push it to its limits. Unless one fought for every patient with all the powers at one's command, one would be only too apt to take a defeatist attitude, to the point of even failing in one's obvious duty. Time and again, the apparently useless life one had saved had subsequently shown itself full of value and meaning.

This attitude was less dogmatic and more reasonable. But, to be rational, we must abandon the absolute imperative in favour of considerations such as a balance of probabilities. If there was a chance, however small, of saving not only life but health, that must be placed on a higher scale of values than the mere prolongation of the automatic action of heart, lungs, and bowels. A few more hours of mental lucidity and capacity to communicate were in a different dimension from months of coma, dementia, or idiocy. Death performed the inestimable office of clearing up a mess too big to mend; if we were going to intervene, then we must have at least some hope of doing that ourselves.

Neurotic Fears

To a psychiatrist many people thought of death in a way that seemed neurotic. Not only were they moved by emotional and non-rational motivations, but they did not face the issue squarely. It had been said that, just as people's minds were in a bad way on the subject of sex at the beginning of this century until Freud had let some light into a dark cupboard, so now we had the same kind of attitude towards death. It would hardly be in better taste to-day to inquire of an elderly man whether he was afraid of dying than, in the days of Victoria, to have opened a conversation with a young lady on the subject of the physical relationship of the sexes. Indeed, the possibility of a fatal outcome was hardly ever discussed between doctor and patient, even when illness had set the plainest signpost. Most doctors felt it kindest to refrain from telling the patient of the facts and the probabilities, and maybe they were justified; though they would surely regard themselves in honour bound to give a plain and honest answer to a straight question, if it were ever put. There, however, the patient himself very often failed. Even the greatest were affected by that weakness, nor were medical men themselves immune.

A neurotic attitude to death was not a fault limited to our present age; in the past it had been stronger. Looking back from our present viewpoint, we saw generation after generation of the Dark Ages sunk in a state of miserable mental enslavement. Passing the centuries under review, we saw the black shadow lift only slowly. If the fears of Hell had receded, those of death with its funereal pomps had retained their place. The physical aspects of bodily decay had kept their morbid grip on the imagination, and it had needed a robust spirit to overthrow them.

One particular type of temperament was perhaps more than normally susceptible to the fear of death. They were the ruminative obsessionals, of whom a great example was Dr. Johnson. Many of them were weighed down by an oppressive sense of the ineluctable passage of time. The ticking of the clock reminded them that an end approached in measured, unvarying steps. Death hovered over them, casting a shadow that was felt even in youth, and deepened always as time advanced. Everything ephemeral was a reminder; spring was more painful to bear, with its promises doomed to extinction, than were autumn and winter. Only the great enduring things, the mountains, the sea, the stars, perhaps the thought of God, could console.

These people were exceptional; and, though most of us had feelings like this at some time, the moments of oppression were usually short and infrequent. It was not easy to say how far the average man without a religious faith, unread in the stoic philosophers, and with little idea of the part that death plays in Nature's economy, had faced the issue and adjusted to it, or how far he had merely succeeded in pushing it out of his mind. As Dr. Slater saw it, the average man generally refused to give any thought at all to his ultimate end. He accepted it, but turned his back on it as something wholly unpleasant, inevitable, but requiring no mental preparation. Only those whose lives had become ones of active suffering came to think of death as a blessing and a release.

Through a Biologist's Eyes

To the biologist the medical man's idea that death is the chief enemy was misplaced. The light drained from the sky long before the sun set, and we should seek out our opponent at an earlier stage, before his inroads had gone too far. But this was indeed difficult. Senescence was a part of our essential constitution, and not easily defeated. The processes of natural selection, which over other spans of life tended constantly to keep a species vigorous by eliminating the feeble and the diseased from the reproductive cycle, were

here of no assistance. The hereditary constitution predisposing to a deterioration which manifested itself only after the end of reproductive life was at no disadvantage while reproduction was still occurring, and would have its full representation in the next generation. Genes which caused such a constitution were immune to natural selection, and might accumulate indefinitely.

The race itself was potentially eternal; and *sub specie aeternitatis* the senescence of the individual was no disadvantage. Death itself became then a boon to the individual and a benefit to the race, by eliminating the worn out and those whose part had already been played. In human communities, if the aged and the sick did not die within no long span after they had ceased to be self-supporting, the burden on society would become disastrous. The death and the removal from the community of those of an earlier generation had another essential part to play in maintaining the adaptability of the species as a whole. Environments were constantly changing—for the animal world because of the changes wrought by climate and by man, for man by the pressure of his own social development. To cope with these changes the species had to throw up constantly a new team. If we wished the human race to thrive we must acquiesce in the need for one generation to give place to the next.

But that did not mean we should think we already had the best of all possible worlds. There were many reasons for believing that it would be advantageous to man if the rate of exchange of generations were a little slower. Human society would lose little if, with a higher proportion of mature individuals, it became a little more conservative, a little more insulated from the clamour of the hungry generations pressing from the rear.

"A Necessary End"

The position of the biologist asked to contemplate the death of the individual was that this is an end devoutly to be wished. Death played a wholly favourable, indeed an essential, part in human economy. Without natural death, human societies and the human race itself would certainly be unable to thrive. This, said Dr. Slater in conclusion, put a definite onus on the philosopher, the psychologist, and the educationist. They should train the individual to be able to regard his eventual death with open eyes and equanimity. Death at a ripe age should be no occasion for regret or mourning. Illness and accident, not to speak of war, remained the enemies of mankind; but death was not.

A booklet from the General Register Office summarizes cancer statistics for England and Wales for 1901–55. Tables of mortality show that in the last 20 years the total mortality from cancer has increased for men at every age but has declined among middle-aged women. The difference is due to cancer of the lung; while increasing in both sexes, it is much more frequent among men than women. The commonest sites of cancer causing death in 1950–4 were, for males, lung, with 336 per million population, stomach 211, intestine 109, rectum 88, prostate 74. For females, they were breast 182 deaths per million population, stomach 118, intestine 106, uterus 91, ovary 60. About 1% of all people who died from cancer are children aged under 15, and over half of these deaths are due to malignant disease of the blood-forming organs. Considerable regional differences exist in death rates from cancer, though the trends up or down are usually much the same throughout the country. In Wales in 1950–4 mortality from cancer of the oesophagus and stomach was notably high, while mortality from cancer of the lung was low. The north of England also had a high mortality from cancer of the stomach. In all large industrial areas mortality from cancer of the lung in men was notably high. Death rates from cancer of the pancreas, kidney, and bladder were all relatively higher in the south of England than elsewhere.—*Cancer Statistics for England and Wales 1901–55*, by A. McKenzie, with additional material by R. A. M. Case and John T. Pearson, General Register Office, H.M.S.O., 5s. 6d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Anencephalus

SIR,—Your leading article on anencephalus (*Journal*, March 22, p. 695) refers to the seasonal incidence of anencephalic births. The epidemiological findings in Northamptonshire suggest that two other environmental factors are present. Firstly, it appears that anencephalic births occur in groups in different places at different times. This feature was noted 100 years ago[1] and is present to a marked degree in Northamptonshire. Secondly, the incidence of anencephalus is greater in urban than in rural districts; most cases in rural areas are born not far distant from towns. Thus in the years 1956 and 1957, only three of the thirteen anencephalics were born in rural districts. Of these three one was, in fact, born on a housing estate on the Northampton boundary.

Congenital Abnormalities in Northamptonshire, 1944–57

	Total	Boroughs and Local Authority Urban Districts	Local Authority Rural Districts	Ratio Urban: Rural
Live births (1944–56) ..	56,142	29,850	26,292	1·1 : 1
Abnormality (1944–57)				
Anencephaly (including anencephaly with spina bifida) ..	60	41 (36)	19 (17)	2·1 : 1
Hydrocephaly	35	24 (20)	11 (11)	2·2 : 1
Spina bifida (including spina bifida with hydrocephaly) ..	113	65 (52)	48 (44)	1·4 : 1
Congenital heart disease	185	86 (78)	99 (94)	0·9 : 1
Cleft palate, hare lip ..	102	58 (51)	44 (41)	1·3 : 1
Mongolism	98	48 (48)	50 (50)	0·96 : 1

The figures in parentheses represent the number of cases where it was possible to confirm the address of the mother at the time of conception and early pregnancy.

If it is accepted that anencephalic births occur in groups, are more common in winter than summer months, and are related to the density of population, then the possibility of infection as an aetiological factor should be kept in mind.—I am, etc.,

Northampton. M. J. PLEYDELL.

[1] Del-Vesco, P. (1859). *Gazz. med. ital. prov. venete, Padova*, **2**, 149. (Cited by Ballantyne, J. W., *Antenatal Pathology and Hygiene: The Embryo*. Edinburgh, 1904.)

SIR,—In your leading article on anencephalus (*Journal*, March 22, p. 695) there are certain observations on which I should like to comment. Data recorded in the undermentioned paper[1] failed to establish any variation in the incidence of anencephalus between different areas within the regions examined, and by comparison of hospital reports and births in the domiciliary service it was shown, I think conclusively, that the former are unreliable indices of such aetiological factors as might be operative. Malpas,[2] examining the records of approximately 14,000 births in an entirely hospital population, concluded that congenital abnormalities of the central nervous system increased with advancing maternal age and high parity. Record and McKeown[3] also considered these factors were significant. As you intimate, the evidence for seasonal fluctuation in the incidence of anencephalus can only be slender, and in general it may be inferred that an observation of this kind is far more likely to gain credence with the statistician than with the obstetrician. It seems, therefore, somewhat cold comfort to end your leader by the somewhat nebulous remark that "the most useful suggestion which can be made to parents who have had an anencephalic child" is that they should "restrict their conceptions to the winter months."

After an extensive inquiry, I was unable to reach any conclusion other than that "anencephaly appears to have a very constant incidence which seems to be unaffected by locality, parity, and maternal age. The absence of positive differences shows that at the moment and so far as present knowledge goes no environmental factor can be held responsible for its incidence, and, this being so, the question of whether anencephaly is due to hereditary or genetic factors alone is still *sub judice*."[1]—I am, etc.,

Liverpool, 1. H. VINCENT CORBETT.

REFERENCES

[1] Corbett, H. V., *J. Obstet. Gynaec. Brit. Emp.*, 1953, **60**, 907.
[2] Malpas, P., ibid., 1937, **44**, 434.
[3] Record, R. G., and McKeown, T., *Brit. J. soc. Med.*, 1949, **3**, 183.

Cryptococcal Meningitis

SIR,—Since 1955 ten cases of meningitis or epilepsy due to *Cryptococcus neoformans* have been diagnosed and confirmed bacteriologically in Government hospitals in Kenya; they will be fully reported later, but for the possible benefit of others faced with this disease I should like now to record the successful results of treatment of the last two cases with "actidione" (cycloheximide) and polymyxin.

As soon as the diagnosis is established daily lumbar punctures are done, reducing the pressure to 120 mm., and 50,000 units of polymyxin B sulphate is given intrathecally; this is continued until the pressure remains normal or until signs of irritation of the nerve roots appear. In our cases both occurred simultaneously after ten days. Cycloheximide is given intravenously on alternate days, starting with 5 mg. (0.5 ml. of a 1% solution) in 10 ml. of normal saline. Successive doses are increased by 5 mg. until vomiting occurs, when dosage is reduced by 5 mg. below the maximum and held at this level. Both our cases were able to tolerate 15 mg. every other day, and this was continued for three months, by which time the cerebrospinal fluid had been normal for three or four weeks. The only toxic symptom observed was a skin rash in one case which appeared at the end of treatment. The 1% cycloheximide solution must be warmed before injection, as it crystallizes out in the cold.—I am, etc.,

Nakuru, Kenya. L. M. B. NEVILL.

Lung Cancer and Tuberculosis

SIR,—Your annotation (*Journal*, January 4, p. 33) concerning Dr. Percy Stocks's recent work on the urbanization factor in the aetiology of bronchial carcinoma provokes again the question, If urbanization is an important causal factor how is it that the disease is less common in American cities than in rural Britain? In 1949 the mortality rate amongst white males in American cities of one million and over was 288 per million living.[1] The rate at that time in rural England and Wales was even greater—about 300. Although I have no current figures, I suspect that Los Angeles, a city well known for smog, has to-day a lung cancer rate comparable with that of rural North Wales.

Of course, the protagonists of the cigarette-smoking theory will say that it is because the residents of rural England and Wales smoked many more cigarettes over the past 20 or 30 years than the citizens of American cities. This I find hard to believe. After all, America is a tobacco-producing country, and 20 years ago the advertising of cigarettes and tobacco products and their distribution in American cities were certainly greater than in rural England. It may be true to-day that wealthy Americans throw their cigarettes away half-finished, thus inhaling only half the carcinogens, but one wonders if this was the practice during the depression years when even American incomes were restrained and when the predisposition to lung cancer was being laid down. Cigarette smoking and urbanization may well be the most important factors in lung cancer, but there must be other factors operating to account for the marked differences in incidence in the United Kingdom and the United States.

1949 was a very important year for lung cancer in the West, for in the United Kingdom, the United States, and Denmark—involving a total population of more than 150 million white males—the mortality rate for lung cancer in the three countries equalled that for tuberculosis, although the individual rates were very different. The figures were:

	Tuberculosis	Lung Cancer
United Kingdom ..	530	500
United States	250	225
Denmark	160	160

On face value, it appears possible that the reason why the American lung cancer rate is only half, and the Danish rate only one-third, that of Britain may be associated with the fact that the American tuberculosis mortality rate is also only half and the Danish rate only one third that of Britain. During the past 15 years cigarette consumption in the United States has outstripped that in Britain. In 1939 Britons were smoking 1,955 cigarettes per head per annum, and Americans 1,750. In 1950 Britons smoked 2,029 and Americans 3,188.[2] It would be expected therefore that the rate of increase of lung cancer would be greater in the United States than in the United Kingdom. As is well known, the rate of increase has been greater in the United Kingdom. It is perhaps less widely appreciated, however, that the rate of decrease of tuberculosis mortality is greater in the United States. The figures are as follows:

Year	Respiratory Cancer	Tuberculosis	Cigarettes
1940	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{270}{130} = 2{\cdot}08$	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{750}{405} = 1{\cdot}85$	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{1955}{1750} = 1{\cdot}1$
1950	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{530}{260} = 2{\cdot}04$	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{420}{240} = 1{\cdot}75$	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{2029}{3188} = 0{\cdot}6$
1953	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{650}{290} = 2{\cdot}27$	$\frac{\text{U.K.}}{\text{U.S.}} = \frac{280}{135} = 2{\cdot}07$	—

These figures, over a period of 13 years, show how closely the ratios of the two diseases in the two major western countries have followed each other. It has been maintained before[3–6] and also hotly contested[7] that tuberculosis has some relation to cancer. Might not the time now be opportune for a thorough statistical reappraisal of the subject?—I am, etc.,

Cairns, Queensland. T. G. PAXON.

REFERENCES

[1] Gilliam, A. G., *J. nat. Cancer Inst.*, 1955, **15**, 1307.
[2] Tobacco Statistics. *J. roy. Statist. Soc.*, 1952, **115**, 152, 297, 447, 599.
[3] Cherry, T. *Med. J. Aust.*, 1924, **2**, 372.
[4] Ibid., 1925, **1**, 581.
[5] Ibid., 1933, **2**, 197.
[6] Cruikshank, D. B., *Papworth Research Bulletin*, 1939, No. 2.
[7] Berkson, J., *Proc. Mayo Clin.*, 1955, **30**, 319.

Chemotherapy in Primary Pulmonary Tuberculosis

SIR,—I would like to congratulate Drs. J. K. Cameron and J. D. Hay and Mr. L. J. Temple on their recent article,[1] entitled "A Critical Examination of the Role of Surgery in the Treatment of Primary Pulmonary Tuberculosis in Children." I am sure that there will be almost general agreement with their view that surgery for primary tuberculosis in children is only occasionally indicated. I must join issue, however, with their conclusion that "the additional routine use of antibiotics does not seem to offer any advantage" in the treatment of this disease. In their series of cases, apart from the 3% development of adult type tuberculosis, seven cases of skeletal and two fatal cases of meningeal tuberculous complications occurred. Also, in addition to a high percentage of residual lung damage, miliary disease and cavitation occurred in some cases. In my opinion, these complications, although relatively small in number, indicate that routine chemotherapy should have been used for all patients.

There is still a difference of opinion amongst paediatricians concerning the wisdom of treating primary pulmonary tuberculosis with chemotherapy, but in considering this matter it is essential that it be understood what is intended in the treatment of this disease. The modern concept is as follows: (1) The killing or inactivation of as many tubercle bacilli in the body as possible; and (2) the prevention of such serious complications as skeletal or

meningeal tuberculosis. It is still argued that our present chemotherapeutic agents may not be able to kill tubercle bacilli, but surely that does not prevent us trying, because subsequent relapse of the disease in later life is so dependent on this factor.

From their total of 409 cases it can be expected that at least 20 of those who did not receive chemotherapy will relapse in adolescence, and even more in middle or old age. In an effort to reduce this number of possible relapses, I consider that adequate chemotherapy should be used in every case of active tuberculosis. In addition the possibility of preventing such terrible complications as skeletal or meningeal tuberculosis in itself should warrant routine protective chemotherapy.

Those physicians who oppose the routine use of chemotherapy for primary tuberculosis in children nearly always use as their criteria the fact that the rate of absorption of enlarged hilar glands or the clearing of segmental involvement is not accelerated by chemotherapy. They then set out to prove that such residual atelectatic areas cause little subsequent trouble anyhow. If this be true, then surely the most important single factor is whether any tubercle bacilli are left in these lesions or not. We know that adequate chemotherapy can at least reduce the numbers of viable tubercle bacilli and thus reduce the possible chance of relapse, and we also know that such chemotherapy can mainly prevent the occurrence of such complications as skeletal or meningeal tuberculosis. Therefore, why not use it? With the various adequate regimes now available the taking of chemotherapy is not a great hardship, and the possible benefits that it confers surely justify its use in every case of active tuberculosis.—I am, etc.,

Northfield, South Australia. R. MUNRO FORD.

REFERENCE

[1] Cameron, J. K., Hay, J. D., and Temple, L. J., *Thorax*, 1957, **12**, 329.

Tuberculous Pleural Effusion

SIR,—Patients with tuberculous pleural effusions have tuberculosis. That means, we believe, chemotherapy for at least 18 to 24 months. We feel, therefore, that little is gained by reporting on small series of cases, as Pines[1] and Emerson[2] have done recently, particularly if the duration of chemotherapy has been relatively short. On the other hand, an analysis of a long-term follow-up of cases of tuberculous pleural effusion, managed by several workers, after an initial one to two years' chemotherapy would be invaluable.

Since 1955 in the Gurkha Sanatorium of the British Military Hospital, Kinrara, we have followed the active form of treatment advocated by the Army Chest Centre at that time,[3] except that our practice has been to continue chemotherapy for 18 to 24 months, according to whether or not a parenchymal lesion is demonstrable on radiography (including routine tomography).

Besides chemotherapy we advise early and if necessary repeated aspiration, followed by the instillation of intrapleural streptomycin, 1 g. After a fortnight's chemotherapy we add breathing exercises and posture. In some acutely ill patients we refrain from aspirating their effusions until after two to three weeks' chemotherapy, as such cases tend to fill up just as rapidly as in the pre-streptomycin era if aspirated early. Aspiration is stopped for the usual indications, otherwise we usually remove as much as 50 oz. (1.4 l.) at a sitting. We have experienced no trouble from this practice, but the fluid is always withdrawn very slowly.

We give streptomycin, 1 g. intramuscularly daily, and isoniazid, 100 mg. orally twice daily, for 30 to 90 days, depending on the case. Thereafter for the remaining 18 to 24 months both drugs are given together every other day.

These Gurkha patients are kept in bed only if they feel and look ill. Unless in the "acute" phase of their illness, which never lasts longer than four weeks, they start on early ambulation, or, as we call it, "restricted activity." Up to the end of March, 1957, all cases completed their treatment at Kinrara. Now after 9 to 12 months they are transferred to a sanatorium in the Cameron Highlands. Thereafter they spend six to nine months at a rehabilitation centre at Seremban where they receive daily oral P.A.S. and isoniazid. At intervals all patients return to Kinrara for routine check-up, and also for their final assessment on completion of treatment.

Our approach to the treatment of pulmonary tuberculosis is similar. Chemotherapy as described above is given for 24 months in all cases, irrespective of any surgical treatment. Patients are kept in bed as long as they are considered infectious. This is followed by ambulatory treatment in hospital and graded physical activity before transfer to the Cameron Highlands and later to Seremban.

We would prefer to keep patients with cavitated lesions in bed with postural dependency until after closure of their cavities and resection, but Gurkhas cannot understand having to stay in bed when they feel well, so up they get. Early ambulation in hospital is certainly good for morale and in no way retards the progress of non-cavitated disease, and it seems a fair compromise for the cavitated patients.

If for any reason we cannot use streptomycin, we give P.A.S. and isoniazid orally daily for three-monthly periods separated by a month without drugs. We have had no complications of isoniazid therapy, and toxic manifestations of streptomycin have been exceptional. If the latter do occur, they do so early during the daily administration of the drug. All patients have a complete clinical, radiological, and bacteriological review every six weeks.

There is an excellent scheme in progress to eliminate, so far as possible, tuberculosis in the Gurkhas in the British Army. No one is accepted for service with the Brigade of Gurkhas unless a radiograph of his chest is normal. All have a tuberculin test and all negative reactors receive B.C.G. All the others, including employed civilians, are examined at intervals by mass miniature radiography. Finally, every case of pulmonary tuberculosis in the brigade is admitted on diagnosis to the sanatorium at Kinrara, and at the same time a signal is sent to all concerned so that immediate control action can be taken.—We are, etc.,

JOHN MACKAY-DICK.
Kinrara, Malaya. DAVID SLATTERY.

REFERENCES

[1] Pines, A., *Brit. med. J.*, 1957, **2**, 863.
[2] Emerson, P. A., *Lancet*, 1957, **2**, 674.
[3] Mackay-Dick, J., and Rothnie, A. G., *Tubercle (Lond.)*, **35**, 182.

Serial Cholecystography

SIR,—Our thanks are due to Dr. C. Bellamy (*Journal*, March 29, p. 769) for putting into dosages the impressions which many readers will have felt on reading Mr. J. Dudfield Rose's article on serial cholecystography (*Journal*, February 15, p. 360).

Technical and specialized journals nowadays contain many articles by people who are devising elaborate methods whereby a little information may be obtained about some minor point in diagnosis. As far as radiology is concerned we are undergoing a period during which all diagnostic procedures are being reassessed from the point of view of dosage. Some of us feel that new procedures should only be seriously considered when they contribute to a reduction in the dosage of ionizing radiations received by the patient and the population as a whole. In so many cases where elaborate processes are described one is tempted to ask whether benefit is likely to accrue to anybody. The defence for some of these diagnostic radiological procedures is that the dose factor should be considered in relation to the circumstances of a particular case, and the procedure is justifiable where it is being done to determine a particular point of issue.

We should all, radiologists included, be honest enough to decide for ourselves whether techniques of this magnitude (such as serial cholecystography) should ever be performed on the human race. Indeed, it is not beyond the bounds of possibility that the time may come when a radiologist (or any other medical practitioner) may be taken to court for exposing a patient to the hazards of diagnostic radiology without due cause. Leukaemias are occurring which could reasonably be attributed to radiology. Whereas it may be pleaded that (as in ankylosing spondylosis) there is room for argument on the ethical problem of weighing one risk against the other, this defence could hardly be applied in the case of serial cholecystography or in the case of certain more extensive examinations carried out on pregnant women.—I am, etc.,

Worcester. ANTHONY A. VICKERS.

Care of the Epileptic

SIR,—You are to be complimented on your series (*Journal*, March 22, pp. 661–72) on the theme of epilepsy, dealing with its classification, treatment, and the value of electroencephalography in diagnosis. Lord Cohen of Birkenhead (p. 672) also describes very fully its many social problems and covers most exhaustively many agencies, both statutory and voluntary, which can help the epileptic to lead a full and active life. So comprehensive is his survey of these various services that it gives one the impression—quite unintentionally, I am sure—that the rehabilitation and resettlement of the epileptic is comparatively easy and largely a matter of directing the epileptic to the appropriate agency. Here in Scotland it is still a formidable problem.

On the question of superannuation and the statement that "the Civil Service and local authorities already operate their superannuation schemes so that there is no deterrent to the employment of the epileptic," I would require to be convinced of this in practice. The Glasgow branch of the Epilepsy Association recently tried to obtain work for epileptics in the Post Office stamping second-class mail. This was turned down, one of the two reasons given being this difficulty of superannuation. One other small point: the children's officer is almost always a chief officer of the children's committee and not (unfortunately) an officer of the health and welfare committee of the local authority, although Lord Cohen did say health and welfare authorities.—I am, etc.,

Dundee. A. MAIR.

Lymphadenoid Goitre

SIR,—I was interested to read Mr. R. L. B. Beare's study of lymphadenoid goitre (*Journal*, March 1, p. 480), and I should like, if I may, to offer certain comments. I was particularly interested in Mr. Beare's experience that the administration of thyroid may lead to arrest or regression in the pathological changes of Hashimoto's disease, as some years ago I was led to believe that such treatment was logical,[1] although I have not myself had the opportunity to put it into practice. My suggestion sprang from a concept of the disease which may be of some interest to Mr. Beare and his readers in so far as it is compatible with the Roitt reaction, and indeed would appear to be strengthened by this recent discovery.

The concept was based on the following considerations: (*a*) Replacement of normal thyroid epithelium by Askanazy cells is constantly associated with lymphoid infiltration. (*b*) These changes are found most frequently in toxic goitres on the one hand and in Hashimoto's disease on the other, although they are also found in non-toxic goitres and are fairly common in otherwise normal thyroids in elderly women.[2] (*c*) These changes are associated with diminution of thyroid function.[2,3] (*d*) The thyroid in Hashimoto's disease is hyperplastic in the sense that the total amount of epithelial tissue is increased.[4]

We are thus confronted with the paradox of hyperplasia associated with hypofunction. Hyperplasia implies increased stimulation from the pituitary, and, as for hypofunction, there is evidence that the Askanazy cell is one of low functional activity. Friedman[5] regarded the lymphadenoid reaction as being a form of cellular involution following prolonged hyperplasia, and indeed observed the progress of the histological picture from hyperplasia to Hashimoto's disease in one patient over a period of eight years. Hyperplasia does not, however, necessarily imply hyperthyroidism; and one might regard Askanazy cell metaplasia as a mode of failure in thyroid epithelium which for some reason is incapable of sustaining the level of activity demanded of it.

The missing link in this concept, so far as Hashimoto's disease is concerned, is the initiating factor in the cycle of hypofunction, hyperplasia, involution; and it is possible that Roitt's observations supply the missing factor. The chain of events might thus become: an antigen-antibody reaction destroying thyroglobulin and reducing the amount of circulating thyroxine; hyperplasia due to increased pituitary stimulation; cellular failure and Askanazy cell metaplasia.

Finally, it would appear doubtful whether the antigen–antibody reaction described can be regarded as the sole cause of lymphoid infiltration, unless it is shown that such a reaction can take place in patchy, focal form; certainly the lymphadenoid–Askanazy cell complex is frequently found in focal distribution in conditions other than Hashimoto's disease. Aetiological considerations aside, however, there would appear to be considerable promise in the Roitt reaction as a diagnostic aid, and as a means towards a better understanding and more logical treatment of an intriguing disease.—I am, etc.,

Giffnock. DOUGLAS R. K. REID.

REFERENCES

1 Reid, D. R. K., *Postgrad. med. J.*, 1951, **27**, 185.
2 Lennox, B., *J. Path. Bact.*, 1948, **60**, 295.
3 Whitesell, F. B., and Black, B. M., *J. clin. Endocr.*, 1949, **9**, 1202.
4 Parmley, C. G., and Hellwig, C. A., *Arch. Surg. (Chicago)*, 1946, **53**, 190.
5 Friedman, N. B., *J. clin. Endocr.*, 1949, **9**, 874.

SIR,—I was very interested in Mr. R. L. B. Beare's paper on lymphadenoid goitre (*Journal*, March 1, p. 480). His suggestion that overactivity of pituitary thyrotrophic hormone may play some part in the increased proportion of ^{131}I-labelled thyroxine in the blood is in accord with observations we have made in two patients with exophthalmic ophthalmoplegia who had no other features of thyrotoxicosis and "low normal" results in tests of thyroid function. They both did have, however, a relatively high serum protein-bound radio-iodine at 48 hours after a tracer dose of radio-iodine (see Table).

	Protein-bound ^{131}I (% of Administered Dose per litre)	B.M.R.[3] (%)	"T" Index	Thyroid ^{131}I Clearance[3] (ml./min.)	24-Hour ^{131}I Uptake (% of Administered Dose)
Mean of euthyroid range[6] ..	0·07	0·5	6·6	21·9	35·6
Case I ..	0·26	−16	1·9	17·0	26·7
" II ..	0·18	−9	2·2	10·7	19·6

I was surprised that Mr. Beare regards the serum cholesterol as a poor index of thyroid function. He is concerned with the diagnosis of the hypothyroid state; we have found[1] the test to be almost as good as the B.M.R. and suitable radio-iodine tests ("T" index,[2] or 24-hour radio-iodine uptake) in confirming this disorder. It is worth noting that other diseases associated with hypercholesterolaemia are rarely involved in the differential diagnosis of hypothyroidism. Mr. Beare considers that thyrotoxicosis was not present in a patient (his Case 11) whose B.M.R. fell from plus 13% (Aub–Du Bois standards) to minus 1% after pre-operative treatment with iodine. There are two reasons for regarding these results as confirming the clinical diagnosis of thyrotoxicosis. Robertson and Reid[3] have shown that the normal range in the United Kingdom for the Aub–Du Bois standards is from 0% to minus 20%. The value given by Mr. Beare corresponds to about plus 23% on the Robertson and Reid standards, and is therefore well above the range of normal variations. Apart from this, whatever the initial value of the B.M.R., Means[4] and Robertson[5] have shown that the B.M.R. falls after iodine therapy in thyrotoxicosis but not in normal or euthyroid individuals.

—I am, etc.,

London, W.6. I. J. L. GOLDBERG.

REFERENCES

1 Goldberg, I. J. L., and Seaman, M. J., unpublished.
2 Fraser, T. R. C., Hobson, Q. J. C., Arnott, D. G., and Emery, E. W., *Quart. J. Med.*, 1953, **22**, 99.
3 Robertson, J. D., and Reid, D. D., *Lancet*, 1952, **1**, 940.
4 Means, J. H., *Ann. intern. Med.*, 1933, **7**, 439.
5 Robertson, J. D., *Lancet*, 1934, **2**, 1076.
6 Bruck, E. K., and Goldberg, I. J. L., *J. Endocr.*, 1958, **16**, 277.
7 Myant, N. B., Pochin, E. E., and Goldie, E. A. G., *Clin. Sci.*, 1949, **8**, 109.

Obese Children

SIR,—Dr. Harold Cohen's observations and hormone assays in adipose children (*Journal*, March 22, p. 686) are very welcome and it is to be hoped that they will be extended by him. For example, do the 17-ketogenic steroids in these children return to values above normal if the calorie intake is increased to normal or average, after a period of low calorie intake, or must the calorie intake be excessive to produce this result? Does an excessive calorie intake produce high 17-ketogenic values in all children, or only in

certain groups of children, and, if so, have these groups certain characteristics? In so far as semi-starvation caused a reduction of high 17-ketogenic values to normal or below normal in fat children, the latter being comparable to its effect in normals, is it valid to conclude that high calorie intake results in functional and persistent pituitary-adrenal hyperfunction? It may be, or it may not.

Under the prudent heading of speculation, Dr. Cohen suggests that increased growth and earlier puberty could be explained on the basis of augmented pituitary activity secondary to overeating. It so happens that whereas the adipose girls in my groups (adipose gynism) tended to have early puberty, the adipose boys (adipose gynandrism) tended to have late puberty and sometimes late descent of the testicles. They also had a number of clinical characteristics and a type of behaviour pattern. The adiposity frequently started at the time of puberty, and in some males a later adolescent androgenic phase with hirsutism and spurts of growth was accompanied with considerable loss of fat without any dietary changes. These clinical considerations, however, are not really the immediate concern of Dr. Cohen's valuable observations, and some of his speculations may prove well founded. Accepting them for the moment, there seems to have been a shift from a position of "no endocrinology in adiposity" to one of "secondary pituitary-adrenal hyperfunction," with all its sequelae and implications. This seems to me to be "progress," even if it is not the end of the road.—I am, etc.,

London, W.1. S. LEONARD SIMPSON.

Ministry Memorandum on Blindness

SIR,—In his letter (*Journal*, February 22, p. 462) Mr. G. M. Barling takes rather a *laissez-faire* attitude to glaucoma. American statistics suggest that 3% of patients over 40 have this disease. In a population, therefore, which is ageing and where the general trend is to longer life I do not think that we can afford to be nonchalant about this.

I agree that it would be impossible for ophthalmic surgeons in their present numbers to examine every patient in the country over the age of 40 periodically to exclude glaucoma. On the other hand our colleagues in pathology do not personally carry out every Wassermann test which is performed in this country. They have technicians who take the blood, set up the test, read it, and transfer the results to paper to be interpreted by medical men. This is a good comparison to make, because if this latter test produced a positive result in 3% of the community it would indeed be a grave outlook.

It is probably asking too much to expect the preventive medicine services of this country to undertake perimetry and tonometry on this vast scale, but I see no reason why ophthalmic opticians should not be trained to do this. They already carry out the large bulk of refractions in patients over 40 and they provide the premises to do this work. I would suggest that all of them should be offered a short course at glaucoma clinics and that when a sufficient number have been trained in this way the Supplementary Ophthalmic Service fee paid to them for refraction work should be augmented for patients over the age of 40, who could then have these time-consuming tests carried out by appointment at a place of their own choosing and without the tedium of having to attend hospital unless they proved suspect of the disease.—I am, etc.,

Birmingham, 13. L. H. G. MOORE.

"Butcher's Thigh"

SIR,—In your issue of November 30, 1957 (p. 1309), which has reached us here, I was interested to read the letter by Mr. J. R. S. Paterson on the subject of "butcher's thigh."

Whilst working in Newcastle upon Tyne I had occasion to deal with two cases of such thigh stabbing in the space of eight days. The first case was a boy of 15 who, whilst engaged in boning a ham, stabbed himself in the right thigh. The skin wound was approximately 1 cm. in length and had not involved any of the great vessels. A week later a young man of 22 was admitted at the point of death, having similarly been engaged in boning beef and having stabbed himself in the upper right thigh. On this occasion the wound had involved all of the four great vessels at the apex of the femoral triangle, making in each of them a lateral incision situated just to the medial side of the vessels, but inclining laterally and very nearly severing the profunda artery. A distressing feature of this accident was the complete absence of knowledge of elementary first aid shown by the staff in the butcher's shop and also by the ambulance driver and his attendant. Fruitless attempts at applying a high tourniquet were apparently made, but no one thought of applying direct digital pressure—a measure which would almost certainly have been life-saving.

I had not heard the expression "butcher's thigh" before, but sought amongst my colleagues in Newcastle information regarding an anatomical point which was referred to as "the butcher boy's point." This is situated at the apex of the femoral triangle where the superficial femoral vessels and the profunda femoral vessels lie one above the other, thus: femoral artery, femoral vein, profunda vein, profunda artery, in that order from before backwards. As Mr. Paterson has done, I too sought amongst some of the local butchers for information regarding the appreciation of this hazard and also inquired as to whether specific legislation under the aegis of workmen's compensation had been laid down to protect butchers and butchers' apprentices from this injury. I found that a heavy leather apron had been designed with reinforced groin pads to be worn when the butcher was dealing with carcasses hanging on hooks. Similarly, I found that when engaged in boning beef or hams the butcher ought to bone away from him or work on a bench which is protected by a suitable guard. It would appear, however, that these precautions are not enforced by law, and only in certain institutions where the hazard is well appreciated have any precautionary measures been taken.

I further recall an instance, again in Dundee, where Mr. Paterson had his experience, of a fatal case of a butcher boy stabbing himself in the groin. I made inquiries regarding the origin of the phrase, "butcher boy's point," but was unable to discover whence it originated or who first coined the phrase. Like Mr. Paterson, I would be very grateful to learn through the medium of your columns any details concerning this injury which your readers may have.—I am, etc.,

Fort William, Ontario. J. C. CAMPBELL.

Sickle Cells and Salmonellae

SIR,—Dr. W. H. Jopling in his letter on this subject (*Journal*, February 1, p. 279) asks if there are any records of salmonellosis complicating haemolytic anaemia. Davidson and Fullerton[1] reported the case of a woman aged 25 years who suffered from a latent haemolytic anaemia and who contracted *Salmonella dublin* infection which precipitated a haemolytic crisis. After one relapse she was treated with blood transfusion and then subjected to splenectomy. The histology of the spleen was described as typical of acholuric jaundice. Kauffmann and Burón[2] described a case of salmonellosis which occurred in a rather obscure case of anaemia.

It is a well-established fact that salmonella infection readily occurs in patients suffering from serious disease, and I have been impressed with the ease with which persons suffering from disorders of the blood and reticulo-endothelial system have become infected by salmonella organisms in both sporadic and epidemic infections in hospital wards. I have personally studied two cases of malignant reticulosis and one case of aplastic anaemia which terminated fatally,[3] and there are a number of references in the literature of cases of leukaemia which became infected by salmonella organisms.[4 5]—I am, etc.,

London, N.W.1. GEOFFREY W. STOREY.

REFERENCES

1 Davidson, L. S. P., and Fullerton, H. W., *Quart. J. Med.*, 1938, **7**, 43.
2 Kauffmann, F., and Burón, F. A., *Ztschr. Hyg. Infekt.-Kr.*, 1935, **117**, 650.
3 Storey, G. W., *The Pathology of Salmonella Food Poisoning*. University of Liverpool M.D. Thesis. 1954.
4 Tegelaers, W. H. H., Veeneklaas, G. M. H., Clarenburg, A., and Vink, H. H., *Ned. T. Geneesk*, 1948, **92**, 1919.
5 Saphra, I., *Amer. J. med. Sci.*, 1950, **220**, 74.

Indications for Hypotensive Drugs

SIR,—What are the indications for hypotensive drugs such as mecamylamine? Various authorities have quoted a number of indications, but the findings when the following patient was readmitted recently have raised doubts in my mind about the problem.

A male Chinese coffee-shop owner aged 40 was first admitted on February 20, 1957, complaining of headache and "high blood pressure." He had been aware of "high blood pressure" throughout the previous six months and had seen many doctors on this account. He admitted becoming worried when a friend also aged 40 had died some months ago from "high blood pressure." As the friend was fat, the patient dieted and reduced his weight from 168 lb. to 147 lb. (76 to 57 kg.). He also gave up red meat (which the Chinese regard as bad for high blood pressure). Worry over his work aggravated his headache, which was constant, though worse in the evenings. There was no undue breathlessness and no recent change in urinary habit. The diastolic B.P. was 130 on admission but fell to 110 with bed rest and phenobarbitone. The heart was not enlarged clinically or radiologically (cardio-thoracic ratio 12.5:26). The E.C.G. was normal. The fundi showed narrowing of arterioles and nipping of veins at arteriovenous crossings, but no haemorrhages or exudates were seen and the disks were normal. Neurological examination was negative. The urine contained a trace of albumin on admission, but subsequent specimens contained no albumin. Blood urea was 49 mg. per 100 ml., and Hb 104%. I concluded the main element of his complaint was due to anxiety. He was reassured and his private practitioner was recommended to give him phenobarbitone. Hypotensives were not regarded as indicated.

He was readmitted on January 23, 1958, with similar symptoms, but, in addition, had been breathless on exertion for the previous four months and his vision had become blurred during the last three months. Diastolic B.P. was now sustained at 150–155. He had bilateral papilloedema with retinal haemorrhages and exudates. The heart was grossly enlarged in the chest *x*-ray (cardio-thoracic ratio 17.5:26) and the lung fields were plethoric. E.C.G. showed a left ventricular strain pattern. The urine persistently contained albumin; blood urea was 50 mg. per 100 ml.; Hb 85%.

Anxiety about "high blood pressure" (much of it iatrogenic) is very common in hospital practice here in Penang. Probably the majority of patients seen in hospital with diastolic hypertension did not have the requisite intelligence or temperament to co-operate in long-term effective therapy with the methonium hypotensive drugs. In most instances one therefore felt justified in awaiting the damage hypertension might (or might not) do before embarking on long-term methonium treatment. However, results in hospital with mecamylamine have been very much more satisfactory regardless of the patient's co-operation. If one individual can progress in less than a year from what appeared to be "incidental hypertension" to malignant hypertension with left ventricular failure, are not the present commonly accepted indications for hypotensive drugs equivalent to locking the stable door after the horse has bolted? Yet how can one determine which horses are going to bolt without further increasing iatrogenic "high blood pressure" neurosis?—I am, etc.,

Penang, Malaya. H. A. REID.

Azacyclonol in Schizophrenia

SIR,—The conclusions drawn by Drs. S. Gray and A. D. Forrest (*Journal*, February 15, p. 374) on the merits of azacyclonol in chronic schizophrenia would seem to require critical study, as they are at variance with the conclusions of others in this field. It would be unfortunate if this valuable drug was damned on inadequate grounds. The authors themselves recognize the flaws in their inquiry, but nevertheless come to a firm conclusion. The difficulties inherent in the trial of any drug in chronic schizophrenia are great, but they are not resolved in this study. The charting of patients as being not changed, improved, or worse is not really informative by itself. This is a clear case where the addition of more examples of case records would have been more enlightening.

One would not expect dramatic changes in a patient who had been schizophrenic for many years even although the drug used did in fact strike at the root of the schizophrenic process. The patient has become habituated to his way of life; and something more than drug therapy is needed to show the changes wrought. Ferguson,[1] among others, has noted the need for psychotherapy to help the patient use his new psychic energy in a constructive manner. It is of interest that Drs. Gray and Forrest noted increased activity in some of their patients, but made no comment on the therapeutic implications. The trial of azacyclonol and a placebo plus psychotherapy would have been more rewarding. It is also of note that the dose of 60 mg. a day used in their controlled trial was much below the 100 to 200 mg. per day which is generally recognized to be the optimum dose. However, Drs. Gray and Forrest used the larger doses in their two illustrative cases.—I am, etc.,

Stirlingshire. W. B. WRIGHT.

REFERENCE

[1] Ferguson, J. T., *Antibiot. Med. Brit. Ed.*, 1956, **1**, 75.

Epistaxis

SIR,—Dr. I. H. J. Bourne's letter (*Journal*, January 18, p. 161) raises some useful points. I have, however, found no better treatment, especially for the surgically inept, than that devised by Mr. T. B. Layton at Guy's Hospital. I have used this a number of times with great success even where elaborate packing failed. Layton's treatment depends upon his contention that in nose bleed which continues beyond the ordinary time by far the commonest cause of this is because the patient, by vigorous swallowing movements, detaches the incipient clot. Some people, he felt, were more determined and repeated swallowers than others, since they objected to blood running down the back of their throats. Proceeding from this, the patient is sat up in a chair and leans forward. Pillows are put behind him and he is supported by them. A cork is then placed between his front teeth and the patient bites on it. If necessary a sedative can be given. The cork, of course, prevents the patient from swallowing. Blood runs forward into the bowl, and in my experience bleeding stops in an extremely short time. The patient can doze comfortably in this position, and, of course, if he needs liquids Dr. Bourne's suggestion of the straw is an excellent one.

I have always been surprised to find how few know of Layton's method for nose bleed and consequently resort to heroic measures with which they are unfamiliar. Patients are greatly relieved by this simple, reassuring, and remarkably successful treatment which requires no pushing and prodding. I have always been grateful to the originator, being very ham-handed myself.—I am, etc.,

Weyburn, Saskatchewan. HUMPHREY OSMOND.

From Operating Table to Bed

SIR,—I am in full agreement with the sentiments expressed in Dr. S. L. Peltz's letter, "From Operating Table to Bed" (*Journal*, March 8, p. 581). For some time now I have emphasized to nurses and anaesthetists in training that one of the most important parts of an operation is the end, and that it is just at this point, when attention is relaxed and minds wander, that troubles can and do occur. Not only can injudicious handling of the patient cause a "shock-like" state, but, as pointed out elsewhere,[1] patients (especially the elderly and those after long operations) "are often unable to cope with the physiological disturbances of the cardiovascular system which are a notable feature of the post-operative phase."

It has long been the practice at the Camberwell Group of Hospitals to transfer all such people to their beds in the operating theatre and to keep them close at hand until we feel that they are adjusted to their new environment. The bed must still, of course, be moved gently and lifts, etc., negotiated with care. We have found that ward

sisters have been happier about their patients and emergency calls to the wards fewer. All this has often appeared to be tedious and time-consuming, but the results have paid dividends, and it helps, too, to deal with some of the difficulties occasioned by shortage of nursing staff on the wards and of personnel trained to deal with unconscious and/or shocked patients. This is no mean consideration on busy operating days.

The solution lies, of course, in a properly staffed recovery ward adjacent to every operating theatre—an ideal to be realized only in the distant future for so many hospitals. Meanwhile these other methods are proving satisfactory alternatives.—I am, etc.,

London, S.W.11. C. D. T. JAMES.

REFERENCE

[1] James, C. D. T., and McCrae, A. N., *Med. Press*, 1954, **231**, 334.

Achalasia of the Cardia

SIR,—I was most interested to read the paper on cardiotomy (Heller's operation) for achalasia of the cardia by Drs. E. D. Acheson and G. D. Hadley in the *Journal* of March 8 (p. 549). I had only in the previous week received an unsolicited testimonial from an old patient upon whom I had performed this operation over five years ago and who had left the district. He writes to say that whereas he was once 7 stones (44.5 kg.) he is now 12 stones (76.2 kg.) and has no difficulty whatsoever with meals, except overdone pig's liver, of which he is particularly fond. There is no doubt about it that from this man's description he would certainly fall into the category of a successful case in the patient's own estimation. The purpose of his writing was to offer to reassure any prospective patient undergoing similar treatment.

In the few other cases under my care the results have been similar, and it always amazes me that such a simple procedure should be followed by such dramatic results, as, in contrast to Ramstedt's operation for congenital pyloric stenosis, there would appear to be no obvious muscle hypertrophy. It is strange that this operation has taken so long to become established in this country.—I am, etc.,

Bath. C. PATRICK SAMES.

Aphthous Ulcers

SIR,—I read the paper on aphthous ulceration of the mouth (*Journal*, March 15, p. 603) by my friends and colleagues Drs. S. C. Truelove and R. M. Morris-Owen with great interest, having suffered with this condition periodically myself for some years. Indeed, I must confess my identity with the one case of failure described in their series, but, in this instance, treatment with hydrocortisone was only instituted at a late stage, as I had already tried cauterization with silver nitrate, local application of chromic acid and hydrogen peroxide, painting with sulpharsphenamine, and taking large doses of vitamin-B complex and ascorbic acid—all to no avail. However, this one failure may even have enhanced the value of the series, since claims of 100% success with any novel form of treatment tend to be regarded with some scepticism by the cynical.

Some of your readers may be interested to know that I have recently had an opportunity to perform a controlled experiment. About 10 days ago three ulcers appeared simultaneously in my mouth, one on either side in the classical position opposite the molars and a third inside the upper lip opposite the second left incisor. On the third day I commenced treatment of the latter alone, because it was the most painful and the most accessible. A hydrocortisone tablet was placed between the ulcer and the gum on retiring to bed on two consecutive nights and allowed to dissolve as I slept. The relief from pain was immediate, and all sign of the ulcer had gone in a further two days. The two untreated ulcers I still have, although they are just beginning to resolve spontaneously.—I am, etc.,

Oxford. M. J. V. BULL.

Plasma-cell Mastitis

SIR,—With reference to Mr. B. N. Colabawalla's recent report of a case of plasma-cell mastitis (*Journal*, December 7, 1957, p. 1352), Mr. R. V. Liddell has suggested that I should record the following case which was recently treated in Stracathro Hospital.

The patient was admitted from a mental hospital, a hard mass being accidentally discovered in her left breast when she was being bathed. So far as is known (she was unable to give any history whatever) there had not been any episodes of inflammation, and the patient's menstrual periods were normal. Again, so far as is known, she had not had any children. Her age was 49. The swelling was situated just above the nipple, with some reddening and induration of the overlying skin but without any actual fixation of skin to it. It was not attached to the pectoral fascia and measured about 2 in. (5 cm.) in diameter. There was no discharge from, or abnormality in, the nipple, and no glands were felt in the axilla or the neck. The swelling was very hard in consistence and was more readily palpable with the flat of the hand pressing it against the chest wall. A presumptive diagnosis of carcinoma was therefore made and a simple mastectomy performed.

Dr. H. L. D. Duguid, pathologist, Maryfield Hospital, Dundee, reported as follows: "The lesion is an area of chronic inflammation showing large numbers of plasma cells and much concomitant fibrous tissue reaction. Adjacent breast tissue shows lobular atrophy and stromal hyalinization. The features are those of reaction to duct obstruction, with subsequent duct rupture and leakage of secretion into the surrounding tissue—the so-called 'plasma-cell' mastitis." The wound healed without complications.

—I am, etc.,

Brechin, Angus. K. JOHN DENNIS.

Cold Humidifiers for Croup

SIR,—May I plead for the use of cold humidifiers in the treatment of croup and bronchiolitis, at least in hospital? The danger of the old-fashioned steam kettle is well recognized, yet it still causes accidents, as reported recently in the daily press,[1] when damages were awarded for scalds resulting from its use.

Humidity of 100% can be obtained if a simple nebulizer is placed inside an oxygen tent. Its use has the advantage of producing humidity and, in addition, an oxygen tension of up to 60% saturation, when oxygen is used as the vector. This can be increased to 80% if a second source of oxygen is led directly into the tent. Many of these infants with laryngo-tracheitis or bronchiolitis are hypoxic and consequently very restless, although they may not appear cyanosed.[2] When placed in humidity and oxygen they rapidly quieten and go to sleep. If treated in a hot steam tent, with no oxygen, they are restless, frightened, and sometimes maniacal. In North American hospitals a specially designed "croupette,"[3] which incorporates the humidifier as an integral part of the tent, is used in the treatment of these respiratory diseases. It seems a pity that such a tent is not more generally known in this country.—I am, etc.,

London, S.W.3. ANN M. PEACH.

REFERENCES

[1] *The Daily Telegraph*, January 30.
[2] Morrison, Brenda, *Lancet*, 1955, **2**, 737.
[3] Turner, J. A., *Canad. med. Ass. J.*, 1954, **70**, 401.

Obscure Abdominal Pain

SIR,—I should like to support Mr. F. R. Brown's plea for a more logical interpretation of the site of abdominal pain (*Journal*, February 22, p. 462). Failure to realize the important principle which he has so often and so well emphasized has led and apparently still leads to errors in diagnosis, so that I have removed spinal tumours from patients who have had appendicectomies, cholecystectomies, and renal explorations carried out in the mistaken impression that the root pain produced by the tumour was arising in the organ for which the needless operation was performed. Such lamentable mistakes would be avoidable if a little more thought were given to the site and nature of abdominal pain.

—I am, etc.,

Cardiff. LAMBERT ROGERS.

Disease Education by the B.B.C.

SIR,—So the vast armies of neurotics who so voraciously lap up and take unto themselves the symptoms hammered out in the patent medicine advertisements ("tired blood" seems to be one of the latest) are to be provided with a more sumptuous feast by the B.B.C. So far they have been given brain tumours, heart disease, tuberculosis, and cancer to chew over. Like medical students and cowards they have died not once but many times, and, if this sort of stuff continues, will die many more.

Last week a man came in a very distressed state because he thought his diplopia (of a simple ocular origin) was inevitably due to a brain tumour; nor had he been reassured by hearing that a *percentage* of brain tumours could be cured. Again, recently a youth in good physical health demanded a chest *x*-ray ("in case he had a growth or something"). It is only three months since I managed with great difficulty to persuade him that he had not got venereal disease.

Serious illness is a personal affair. The fear and distress that accompany it are to be dealt with personally by the physician with all the energy and optimism he can muster. The public is a suggestible busybody, with more than a streak of sadism about it.

Some bogies have already escaped; let the B.B.C. quickly put back the lid on the Pandora's box they have opened. Let them take us instead, as they do so well, away from our tummies and headaches, and outwards on paths of high adventure, preferably in the sunshine.—I am, etc.,

Tunbridge Wells. A. CAMERON.

SIR,—It has been argued that patients will benefit by being taught about disease, but the greater understanding of doctors and nurses does not make them better patients when they are ill. In fact they are filled with ideas of rare complications, and think in terms of the worst course the illness might take. They worry about the differential diagnosis, and lack the faith which the more ignorant lay patient may possess that the adviser has superior knowledge and is to be trusted when he is reassuring.

Not everyone has a robust mental digestion, and food for thought should not be indiscriminately distributed. In teaching the public about disease the B.B.C. are helping to replace faith by fear. They should confine their propaganda to preventive medicine, and someone responsible should be placed in charge.—I am, etc.,

Paignton, Devon. J. F. BURDON.

Television Casualties

SIR,—Television casualties are not confined to the human race. Our golden retriever, an ardent viewer, was watching a programme about Pasteur's work on hydrophobia, during which a rabid dog was shown being experimented upon. Our dog promptly turned away from the set and vomited her dinner.—I am, etc.,

Reading. A. G. LESLIE-SMITH.

POINTS FROM LETTERS

Treatment of Chilblains

Dr. ALBERT E. NICHOLLS (Shrewsbury) writes: Following a conversation with another doctor whose wife had derived great relief, I have for the past few years given tab. nicotinamid., 50 mg., thrice daily during the winter, and the same patients come each late autumn for a winter supply. Judged from patients' experience, they are the best tablets I have tried. Moreover, they have the great advantage of being harmless and free of side-effects.

Doctors and Human Survival

Dr. C. C. M. WATSON (Merioneth, N. Wales) writes: Dr. Felix Brown's rather naive letter about atomic weapons (*Journal*, February 1, p. 283) shows the muddled thinking that is so common even among educated people when discussing these matters. The problem facing us is the age-old one of peace and war rather than the particular weapons used at the time. The fact that atomic weapons are so much more destructive than previous weapons merely makes the problem more acute; it does not mean that the problem is a new one—how to prevent war.

Obituary

HECTOR CAMERON, M.D., LL.D., F.R.C.P.

Dr. Hector Cameron, consulting physician to the department of diseases of children at Guy's Hospital, died at his home at Godalming, Surrey, on April 1. He was 79 years of age.

Hector Charles Cameron was born in Glasgow on July 17, 1878, the son of Sir Hector Clare Cameron, professor of clinical surgery in Glasgow University. From Clifton College he went on to Glasgow University and then entered St. John's College, Cambridge, where he was a foundation scholar in science. After taking first-class honours in Part 1 of the Natural Sciences Tripos, he won a university scholarship to Guy's Hospital. Qualifying M.R.C.S., L.R.C.P. in 1905, he took the B.Chir. in 1906, the M.B. in 1907, and proceeded to the M.D. in 1910. In 1908 he was elected a Member of the Royal College of Physicians of London, becoming a Fellow of the College six years later.

Until his appointment to the honorary staff of Guy's Hospital as assistant physician in 1910 Cameron had held a variety of posts at the hospital, including those of demonstrator of physiology, out-patients officer, house-physician, anaesthetist, and medical registrar, and he had also served as clinical assistant at the East London Hospital for Children and the Evelina Hospital for Sick Children. Dr. Cameron's life's work was in paediatrics, and he was placed in charge of the children's department at Guy's as soon as he joined the staff. His hospital meant much to him, and his work for the medical school was outstanding. As early as 1911 he was appointed sub-dean and in the following year dean. In due time he became full physician to the hospital, and when he retired he was appointed consulting physician.

Cameron was a good teacher and an author of distinction. His best-known book, *The Nervous Child*, was first published in 1919, and *The Nervous Child at School* appeared in 1933. He also wrote *Diet and Disease in Infancy* (1915) and *Diseases of Children* (1926). He gave the Lumleian Lectures in 1925, choosing for his subject "Some Forms of Vomiting in Infancy." In his young days he was editor of the *Guy's Hospital Gazette*, and after his retirement he devoted much time to studying the history of the hospital while writing a book entitled *Mr. Guy's Hospital, 1726–1948*. He was also the author of two biographies, *Joseph Lister, the Friend of Man* and *Sir Joseph Banks*.

As long ago as 1910 Dr. Cameron had been honorary secretary of the Lambeth Division of the B.M.A., and he held several other offices in the Association. Having been twice honorary secretary of the Section of Therapeutics, he served as a vice-president of the Section of Pharmacology, Therapeutics, and Dietetics at Brighton in 1913, and at Edinburgh in 1927 he was a vice-president of the Section of Diseases of Children, becoming the president of this Section in 1931 (Eastbourne). He was also a past president of the Section for the Study of Disease in Children of the Royal Society of Medicine, and of the British Paediatric Association. He was a member of the council of the Royal College of Physicians from 1933 to 1935, and an examiner from 1933 to 1937 and again from 1939 to 1943. Two years ago the honorary degree of LL.D. was conferred upon him by Glasgow University.

Dr. Cameron is survived by his wife (formerly Miss Dorothy Hill) and two daughters.

A colleague writes: Hector Cameron's great influence on paediatrics was exerted in two ways. *The Nervous Child* (1919) and *The Nervous Child at School* (1933) were widely read, and through them many doctors began to understand the relation between nervous strains and the symptoms which expressed them. Cameron's version of the under-

lying chemical mechanism seems rather naïve to-day, but it cannot be urged that newer concepts have yet proved to be more useful in this field. The other way in which Cameron's influence was propagated was by personal contact with students, general practitioners, colleagues at hospital, and paediatricians all over the country. He taught students to be selective as well as attentive with eye and ear. His own vision was penetrating and his memory unerring as he picked out from his vast medical experience some observation relevant to the case in hand. He talked aptly, with much humour and free use of anecdote to make a point memorable. At tea after the round a smaller audience would enjoy his wonderful ability as a raconteur and mimic. He was generous with his time and talent—it was typical of him that when he was at the height of his professional success he found time to write to the unknown young author of a short article in this *Journal* an appreciative note pointing out a new facet of the subject.

After he had retired from Guy's Dr. Cameron was asked to return to conduct a ward round with each new children's firm. Those were delightful afternoons, but after two or three years he abruptly refused to come any more, as he said he was getting too rusty. The real reason was that he thought that if he became senile it would embarrass his successor to stop inviting him. In fact there never was the slightest slackening of his mental powers, and he was able to make for himself a new career as an author: his books on Joseph Lister and especially on Sir Joseph Banks were well received; *Mr. Guy's Hospital* expressed local history in a style which concealed the labour of research among dusty archives; the short biographies in the *History of the British Paediatric Association* added posthumous distinction even to those who had managed to avoid it while they were alive. Not all that he wrote was published: there was the biography of Arkwright; despite his romantic scenario the film about Mary Queen of Scots was never made; and during his last illness he wrote a detective story.

This illness was borne with insight and courage, and also with optimism when there was a favourable vicissitude. A few months ago one would have thought that Hector Cameron might have continued his activities for 10 years more, but with the sudden appearance of cardiac symptoms at 79 the outlook changed. He hoped to be better in the summer; he wanted to reach his eightieth birthday and to revisit the Athenaeum; but it was not to be. We are left with the memory of a wise and kind teacher, counsellor, physician, friend, and entertainer. His books remain as his visible monument, but every day that we practise medicine with children we are subliminally affected by his original work, as it was thought out 40 years ago, on the nervous child.

A. W. ALLEN, M.D., D.Sc., F.A.C.S., Hon.F.R.C.S Hon.F.R.C.S.Ed.

Dr. Arthur W. Allen, one of the most eminent surgeons in the United States, died at Boston on March 18, aged 70. He was formerly chief of a surgical service at the Massachusetts General Hospital and lecturer in surgery at the Harvard Medical School.

We are indebted to Sir GORDON GORDON-TAYLOR for the following appreciation: The death of Arthur Allen, to his intimates known as "Jimmy," has removed one who for more than a quarter of a century has played an important part in cementing Anglo-American surgical friendship, and it was fitting that he should be president of the American College of Surgeons when in 1947 the Honorary Fellowship of the English College of Surgeons was bestowed on himself and several other transatlantic master surgeons. Like his great friend Henry Cave of New York, he was a Kentucky man, having been born in McKinney, Kentucky, on November 30, 1887: at the time of his death on March 18 he was therefore little more than 70 years of age. He graduated from Georgetown College, Kentucky, in 1909, and obtained his M.D. from Johns Hopkins in 1913. He was next associated with the Massachusetts General Hospital, Boston, soon served in an advanced field hospital in France in the first war, and ultimately was chief of the East Surgical Service of the "M.G.H." from 1936 to 1948. Subsequently he held consultant posts to the "M.G.H.," and in his later years much of his time was devoted to the Boston Medical Library, one of the most important in the U.S.A. Professional honours were poured upon him, and he held every important office in the surgical colleges and associations of the United States: he occupied the real "surgical woolsack" of American surgery as chairman of the Board of Regents of the American College of Surgeons from 1948 to 1951.

His high reputation in international surgery brought him the Honorary Fellowship of the English and Edinburgh Colleges of Surgeons and also in 1956 the rare award of the Bigelow Medal. He was a foreign member of the Académie de Chirurgie. His own surgical interests were in the abdomen, and he was one of the earlier surgeons to take an interest in the surgical treatment of ulcer haemorrhage and perhaps the first to direct attention to the relationship between age and the need for emergency surgery in these anxious cases. As befitted one who worked in the hospital of Smithwick, J. C. White, and McKittrick, he took an interest in neurovascular surgery, serving on a special committee of the National Research Council in the second world war. He had an authoritative experience of the problem of thrombosis and embolism, so strangely frequent in the hospitals of the New England States, and wrote on ligature of the femoral vein as a prophylactic against pulmonary embolism. The very great interest which I observed in this complication in 1946 in Boston and the frequency of vein ligation aroused the wonder whether this post-operative complication had any relationship to the Halsted technique, when the extreme rarity, or even total absence, of such complications in Bland-Sutton's wards at the Middlesex Hospital is remembered in a class of surgery, especially pelvic surgery, in which these complications are reputedly frequent: patients grew very little older as a result of operations at Bland-Sutton's hands.

Arthur Allen was a delightful man, a kindly adviser to the many young surgeons whose steps I have so often directed to Boston. Wherever he went there was "laughter and the love of friends."

A. F. S. KENT, D.Sc.

Dr. A. F. S. Kent, formerly professor of physiology in the University of Bristol, died at Bath on March 30, aged 95. His description of the auriculoventricular bundle was published in the *Journal of Physiology* in 1893. The same discovery was made quite independently during the same year by W. His, of Leipzig, and the names of both men are therefore associated with this important early investigation of the conduction of the heart beat.

Albert Frank Stanley Kent was born on March 26, 1863. From Magdalen College School he went on to Magdalen College, Oxford. After graduating in the final honours school of natural science, he became a demonstrator of physiology at Owens College, Manchester. He then returned to Oxford for two years before becoming a demonstrator of physiology at St. Thomas's Hospital in 1891. There he worked for the next four years with Sherrington, who was lecturer in physiology. He resigned his appointment in the physiology department at St. Thomas's in 1895, and for the next few years he interested himself in the new technique of radiology, helping to establish the *x*-ray department at St. Thomas's. At a large meeting of the Southern Branch of the B.M.A. in Salisbury in March, 1896, Dr. Kent gave "a lucid exposition of the leading principles" of

Roentgen's discovery and demonstrated the bones of a hand affected with rheumatoid arthritis (*B.M.J.*, March 26, 1896, p. 810).

In 1899 Dr. Kent was appointed professor of physiology in University College, Bristol, and he remained in that post until 1918, nine years after the foundation of the University of Bristol, in which he took an active part. In his early years in Bristol he did much to encourage the study of bacteriology, and he directed the work of the clinical research laboratory in University College and was bacteriologist to Bristol Royal Infirmary. Later he became an authority on industrial hygiene, and during the first world war was the author of two official reports to the Chief Inspector of Factories. The first was on the subject of the investigation of industrial fatigue by physiological methods, and the second was on the influence of overtime on fatigue. This work preceded that of the notable Health of Munition Workers Committee. For some years Dr. Kent edited the *Journal of Industrial Hygiene*. When he resigned from his post in Bristol in 1918 he went to Manchester to direct the department of industrial administration at Manchester Municipal Technical College. When he finally retired he went to live in Bath, where he continued his researches in a laboratory he set up in his own house. He maintained his enthusiastic interest in physiology into extreme old age.

D. ARWYN DAVIES, M.R.C.S., L.R.C.P.

Dr. D. Arwyn Davies, who was in general practice in Carmarthen for thirty years, died at Llandough Hospital on March 8 after a long illness. He was 70 years of age.

David Arwyn Davies was born in London on August 20, 1887, the elder son of the Rev. J. E. Davies, one-time Moderator of the General Assembly of the Presbyterian Church of Wales. He was educated at the City of London School and went from there to Guy's, qualifying M.R.C.S., L.R.C.P. in 1912. After leaving Guy's he became a resident medical officer at the West Herts Hospital, Hemel Hempstead, and later at the County Hospital, Aberystwyth. He was for some years at the 3rd London General Hospital, Wandsworth, and it was there that he worked as a resident to Wilfred Trotter—an experience he always liked to recount and recapture. After a few years in general practice in Gowerton he moved to Carmarthen in 1924 and joined a busy general practice partnership. He also became a member of the medical staff of the Carmarthenshire County Infirmary. In his work as a family physician Arwyn Davies was intensely interested in patients as individuals. His personal and friendly approach to their problems was rewarded by their deep affection and appreciation. During his professional life in Carmarthen he was active in many spheres. He was a keen "B.M.A. man," and in 1938–9 was chairman of the South-west Wales Division. Ill-health later prevented him accepting a Branch presidency. He was a founder member of the Carmarthenshire Executive Council, and served for many years on the St. David's (Carmarthen) Hospital Management Committee. In 1945 he became a justice of the peace for the County of Carmarthen. At one time he was an active Freemason and a Rotarian. Throughout his life Arwyn Davies held strong religious convictions. In the recurring crises of a long illness these convictions must have helped him. In his retirement he loved seeing people and hearing about people. Fortunately his keen sense of humour never left him, and even in the most trying circumstances he could find something to amuse him. Above everything else he was a family man and lived to see his two sons qualify in medicine and to see his elder son win the B.M.A.'s Charles Oliver Hawthorne Prize in 1957. Those who were privileged to know Arwyn Davies mourn the loss of a kindly physician, a staunch friend, and a loyal colleague. Sincere sympathy is extended to his widow and to his two sons, Dr. J. E. Davies, of Winnipeg, and Dr. D. Wynne Davies, of Llandough Hospital.—J. R. E. J.

Medical Notes in Parliament

EMPLOYMENT OF THE DISABLED

The Disabled Persons (Employment) Bill, which gives effect to those recommendations of the Piercy Committee on the Rehabilitation, Training, and Resettlement of Disabled Persons requiring legislative enactment, was given a second reading on March 31. Mr. ROBERT CARR, Parliamentary Secretary, Ministry of Labour, who moved the Bill, found cause for satisfaction in its being a minor measure, since the reason was that the Piercy Committee had concluded that the statutory framework of the services for the disabled was basically satisfactory and needed little if any amendment. In the sphere of employment for the disabled the committee had recorded that the existing services were comprehensive and well established, needing little change or development.

Clause 1, he explained, changed the minimum age at which boys and girls could become eligible for rehabilitation and training courses, and by substituting the school-leaving age for the age of 16 laid down in the 1944 Act made the benefit of training and rehabilitation available for boys and girls immediately on leaving school. Clause 2 made two changes in the scheme of registration of disabled persons. Under the 1944 Act the disability must be expected to last for at least six months if a person was to be eligible for registration. The Piercy Committee thought this did not connote a sufficiently substantial handicap, and suggested that the minimum period should be raised to one year. Subsection (1) amended the 1944 Act accordingly. Subsection (2) removed an anomaly: while the act of registration was voluntary, once a person was registered he could not voluntarily withdraw; the subsection made it possible for a person to have his name removed from the register on written request.

Formal Transfer of Responsibility

Clause 3 and the Schedule contained the main provisions of the Bill. The purpose was to move the relevant powers and duties of the local authorities from the various statutes under which they were held into the Bill, thereby placing them under the formal supervision of the Minister of Labour and the Secretary of State for Scotland. They made no material change in the nature and extent of the powers and duties in the hands of local authorities. Under the National Assistance Act, 1948, these authorities had permissive powers to provide for the welfare of all categories of severely disabled persons. (In respect of the blind these powers are mandatory.) Under the Health Service Acts the authorities had a general duty to provide for the aftercare of the tuberculous. As part of this provision a few local authorities had established sheltered workshops for the tuberculous disabled.

The committee had recommended that the power of local authorities to provide sheltered employment for those disabled who were capable of remunerative employment should be separated from their welfare and aftercare powers; and that these sheltered employment powers should be transferred to the Disabled Persons Employment Act. That was done by the Schedule. But the committee had also recommended that those who were so severely disabled as to be capable only of diversionary work should continue to be dealt with under the welfare provisions of the Assistance and Health Service Acts. It had therefore been necessary to disentangle the sheltered employment powers from the general welfare powers. It was this separation of statutory responsibility for welfare and sheltered employment which made Clause 3 and the Schedule so long and complicated.

Subsection (1) of the clause gave all local authorities power to provide sheltered employment and training for severely disabled persons (section 2 cases, as they were known) registered under the 1944 Act. It also gave the Minister of Labour the power of direction similar to that of the Minister of Health and the Secretary of State for Scotland under the National Assistance

Act. Subsection (2) cancelled existing powers of local authorities under the Assistance and Health Service Acts so far as they were replaced by the new powers under subsection (1). Subsection (3) gave the Minister of Labour responsibility for the general guidance of local authorities and required the authorities to exercise them in accordance with the statutory schemes in the same way as they did now under the National Assistance Act. Subsection (4), and the Schedule, was to secure that when the powers to provide sheltered employment had been transferred they would still be subject to the same regulations as before in matters such as the procedure for submission and approval of schemes, the making of regulations, and the exercise of default powers by the Minister. Subsection (6) provided for the whole of Clause 3 to come into force next January, thus allowing time for discussion with the local authorities and for other administrative arrangements that had to be made.

If the Bill concentrated on streamlining the machinery and concentrating authority in one place, rather than on introducing any dramatic new policies, Mr. Carr believed it would make the machinery more efficient and so enable more power to be put behind the effort to help the disabled.

Need to Remember Medical Features

Mr. SOMERVILLE HASTINGS (Barking, Lab.) commended most strongly Clause 1. It was a good thing to get rid of the waiting period between leaving school and starting training for work as a disabled person. But he was glad it went back only as far as the school-leaving age, because it would be a disaster if occupational training were started too soon. For the disabled more than any others a broad education was necessary. He was not so happy about Clause 2. The most difficult thing a doctor had to do was to forecast the future.

Clause 3, which exercised him most, dropped the pilotage of the Ministry of Health and took on the direction of the Ministry of Labour. He wondered if the outlook of the latter was as health-conscious as that of the former. The problem of the disabled was to a large extent a medical one. Though the change might make for administrative convenience, he wondered if it would not be to the advantage of the disabled if there were a watching brief on health always available for them. In the training of the disabled, in the selection of occupations for them, and in the supervision of their progress, recovery, and capacity for new work, medical considerations must always come in. He hoped that under the new arrangements this would not be forgotten.

ANSWERS TO QUESTIONS

Poliomyelitis Vaccine Supplies

The MINISTER OF HEALTH answered a series of questions on the supply of poliomyelitis vaccine. He told Mr. S. AWBERY (Bristol, Central, Lab.) on March 3 that purchases of poliomyelitis vaccine, including Salk, were being kept under constant review in the light of the number of registrations for vaccination. At the end of February 37% of all the children in Great Britain who had been registered had had two injections and a further 11% their first injection. It was the Government's aim that vaccination should be available by the summer for those in the priority groups who had registered.

Mr. FREDERICK WILLEY (Sunderland, North, Lab.) was informed that, so far, two British firms had produced batches of poliomyelitis vaccine and both were supplying it for use in the vaccination programme. Of the total quantity of vaccine isued to date 62% had been of British manufacture.

Mr. ARTHUR SKEFFINGTON (Hayes and Harlington, Lab.) was told that Salk vaccine was being purchased from both Canada and the United States. So far 2,826 litres had been received and more was on order.

Mr. SKEFFINGTON asked what number of parents, offered the choice of either poliomyelitis vaccine manufactured in the United States or in the United Kingdom, had opted for the latter only. Mr. WALKER-SMITH stated that no national figures were available, but his information was that in most areas a large majority of parents had made no objection to Salk vaccine.

Payment for Polio Immunization

Mrs. L. JEGER (Holborn and St. Pancras, South, Lab.) asked what payment was being made to general practitioners in connexion with poliomyelitis immunization; what was the total estimate of this amount; and whether this sum would be deducted from the central pool available for the payment of general practitioners.

Mr. WALKER-SMITH replied that general practitioners received from the local health authority a fee of 5s. for the record of each course of poliomyelitis vaccination. No estimate of the amount involved was yet available. The sums paid in any year would, like all other payments for services, be deducted from the central pool available for the payment of general practitioners in respect of that year in accordance with the arrangements agreed with the medical profession.

Facilities for Mental Treatment

The MINISTER OF HEALTH has supplied Mr. N. DODDS (Erith and Crayford, Lab.) with a variety of information about existing and projected facilities for the treatment of mental illness.

On March 28 he stated that the total number of hospital beds on December 31, 1956, was 508,228, of which 482,553 were staffed. The number occupied at that date by patients with mental and nervous illnesses was not available, but of the average daily number of occupied beds in 1956 (423,818) 48.2% were occupied by patients suffering from mental illness and mental deficiency.

Mr. DODDS wanted to know what proposals the Minister had for building mental hospitals which would fulfil the modern concept of the treatment of mental illness and deficiency; and what plans he had to modernize some of the older mental hospitals. Mr. D. WALKER-SMITH stated that substantial new building and modernization was in progress or planned at 13 mental and mental deficiency hospitals in addition to developments carried out in recent years, and the inclusion of psychiatric units was being considered in several of the new general hospitals now being planned. The requirements of present-day methods of treatment were constantly borne in mind.

The MINISTER stated, also in reply to Mr. DODDS, that the numbers of nursing staff employed at mental and mental deficiency hospitals on September 30, 1957, the latest date for which figures were available, and, for comparison, the numbers on December 31, 1955, were as follows:

	December, 1955	September, 1957	Increase
Total nursing staff:			
Whole-time	26,713	28,443	+1,730 (6%)
Part-time	9,130	9,953	+823 (9%)
Student nurses (included in above):			
Whole-time, male ..	1,708	2,426	+718 (42%)
,, female ..	2,518	3,277	+759 (30%)

The rate of recruitment of nursing staff to mental and mental deficiency hospitals had appreciably improved in the last two years, with a marked increase in the number of student nurses, both male and female.

Mentally Ill Children

What, asked Mr. DODDS, was being done to establish small units throughout the country for giving treatment to children who were acutely ill so as to eliminate the need for placing them in mental hospitals primarily devoted to adults, and sending them so far away as to deprive them of visits by relatives and friends? Mr. WALKER-SMITH told him there were 17 special units for mentally ill children in England and Wales. Ten of these were administered in association with a mental or neurosis hospital; all these were in buildings separate from those used for adult patients. Nine other units were planned or under consideration. Because the number of children who suffered from mental illness (as distinct from mental defect) was fortunately comparatively small, admission to a special unit

might involve sending them farther from home than would admission to the mental hospital serving the area in which they lived.

Reviews of Mental Defectives

Mr. DODDS also asked the Minister what progress had been made in reviewing the cases of mental defective patients with a view to ending compulsory powers, consequent upon the instructions issued on January 16, 1958; what was the number concerned; how the review was being carried out and by whom; what was the rate of progress; when it was expected that the review would be completed in existing cases; in how many cases compulsory powers had been ended; and what was the number discharged from mental hospitals, or under consideration for discharge, as a result of the review up to the latest convenient date. Mr. WALKER-SMITH stated that the review was being carried out by medical superintendents or appropriate medical officers of hospitals and the Board of Control. At March 25 hospitals had submitted 9,122 recommendations, and of these 5,155 patients had been discharged from orders to remain in hospitals on an informal basis. It was not possible to say when the review would be completed or the total of patients concerned.

Sir WILLIAM ANSTRUTHER-GRAY (Berwick and East Lothian, Con.) asked the Secretary of State for Scotland on March 26 whether a review had been made of mentally defective patients detained in Scotland comparable to that under which the Ministry of Health had discharged 814 persons pursuant to the decision of the High Court of March 9, 1956, in the case of Miss Kathleen Rutty. Mr. J. S. MACLAY stated that the orders made by sheriffs placing mental defectives in institutions were made after due inquiry. The General Board of Control had no duty or authority to examine the grounds of a sheriff's order, but they carried out, of course, their statutory duty to review the continued detention of such defectives, after a year and then at three-yearly intervals, having regard to the question whether it would be in the patient's interest to remain in the institution. The General Board of Control for Scotland was, however, considering, with full regard to the differences in the law of the two countries, whether any action was appropriate.

Distribution of Merit Awards

The MINISTER OF HEALTH on March 31 gave Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) the following details about the distribution of merit awards among consultant physicians, surgeons, and psychiatrists in England and Wales at December 31, 1957:

Distribution of Merit Awards in Certain Specialties Between Consultants in England and Wales at December 31, 1957*

Specialty	No. of Consultants	Awards			
		A	B	C	Total
General medicine ..	822	59	151	263	473
Mental health ..	614	6	20	63	89
General surgery ..	863	62	138	256	456

* If a consultant practises in more than one specialty, he has been included in each.

Statement on Senior Registrars

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked the Minister of Health on April 3 if he would state the conclusions reached at his discussions with the Joint Consultants Committee and with their chairman regarding the senior registrar problem. Mr. D. WALKER-SMITH: I saw the chairman of the Joint Consultants Committee on April 1 and he put various suggestions to me. I am considering these, and will make a statement as soon as possible after the Easter recess.

Alcohol and Road Accidents.—The report on alcohol and road accidents has been received, and will be published as soon as possible.

Medico-Legal

SYSTEMATIC THEFTS FROM SURGEONS

A male nurse who posed as a visiting doctor and stole from surgeons' dressing-rooms at hospitals was sentenced to three years' imprisonment at the London Sessions on March 26. He was James Edward Coffey, 26, of no fixed address, who had been sent to the Sessions for sentence from Bow Street on two charges of theft and one of obtaining £10 from the Post Office by means of a forged instrument.

A detective said that Coffey saw a surgeon at the Gordon Hospital, Vauxhall Bridge Road, and told him he was a Dr. Ahmed, from Pakistan. He was given permission to watch an operation and was taken to the surgeons' dressing-room, where he changed into a gown. He then went into the operating theatre and watched an operation for half an hour, leaving before it was finished. Returning to the surgeons' dressing-room, he stole from jackets there.

Coffey was now asking for 13 similar thefts to be taken into consideration, from St. Bartholomew's Hospital, the French Hospital, Guy's, St. Alfege's, St. Mary's, the Chelsea Hospital for Women, and Colindale Hospital. From some of them he had stolen more than once, and in each case had posed as a doctor and watched operations. Coffey had nine previous convictions and had been sent to prison before for posing as a doctor and robbing surgeons in hospitals. At the time of his arrest he was on sick leave from a hospital in Colchester, where he was a male nurse.

Passing sentence, the chairman of Sessions told Coffey: "You have been committing these crimes against hospitals since 1951. There is no excuse for it, and you have been a serious pest to hospitals."

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in February was 124, compared with 86 in the previous month and 99 in February, 1957.

The numbers of cases of industrial diseases in the United Kingdom reported during February, 1958, were as follows: lead poisoning 6, anthrax 1, epitheliomatous ulceration 20, chrome ulceration 15; total 42. There was one death from epitheliomatous ulceration due to mineral oil.—*Ministry of Labour Gazette*, March, 1958.

Scotland in 1957

Though the infant mortality rate decreased from 38.6 to 28.6 per 1,000 live births in Scotland during 1950–7, it remained the same in 1957 as in 1956, according to the latest report of the Department of Health for Scotland.[1] And it is still distinctly higher than in England and Wales, several of the Commonwealth countries, the U.S.A., and Scandinavia.

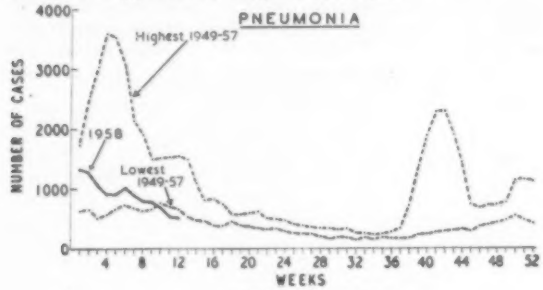
About two-fifths of the hospital beds provided by the N.H.S. are in mental hospitals and mental-deficiency institutions. There are 30 mental hospitals accommodating about 21,000 patients; of these, 15,500 were certified and 5,500 voluntary. The Department of Health comments: "Some concern may, however, be felt at the number of elderly patients dying within a very short time of reaching hospital. Some at least of the old patients dying within a few days of reaching a mental hospital need not have been sent there at all if alternative accommodation with suitable care had been available."

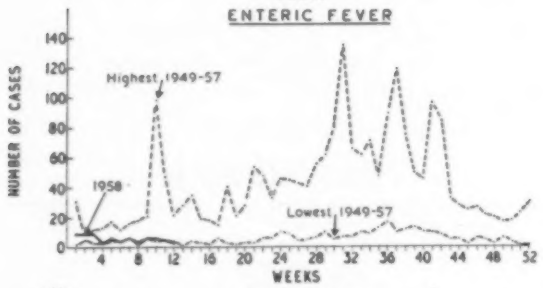
[1] *Report of the Department of Health for Scotland, 1957*, H.M.S.O., 7s.

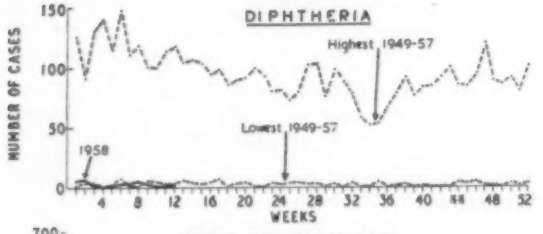
As "an interesting example of what health departments could do," the report cites a scheme at Kilmarnock for the investigation of deaths from coronary thrombosis. The medical officer of health receives reports of them, and it is hoped that the data being collected will ultimately throw light on prognosis and such various aetiological factors as diet, body build, and occupational history.

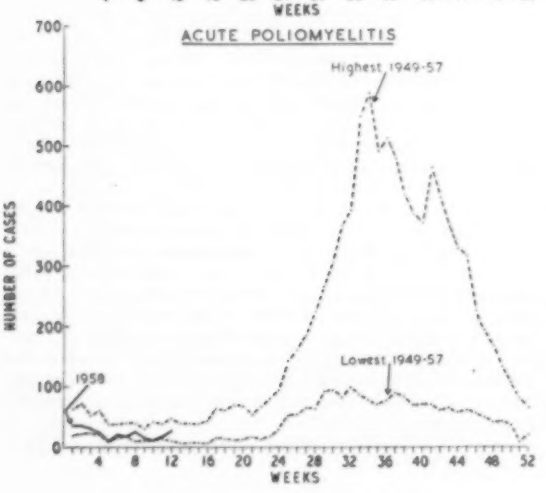
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 22** (No. 12) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	2	0	4	0		3	0	2	0	4
Dysentery ..	1,171	112	214	7	3	1,317	78	250	15	2
Encephalitis, acute	4	0		0		4	0		0	
Enteric fever:										
Typhoid ..	2	0	0	0		1	1	0	0	
Paratyphoid ..	1	0	4 (B)	0	13 (B)	3	1	0	0	
Food-poisoning ..	173	29	8	0		298	22	11	2	
Infective enteritis or diarrhoea under 2 years				7	16				13	14
Measles *	4,631	232	103	38	8	27,179	2034	550	444	217
Meningococcal infection	20	3	11	1	2	30	3	9	2	1
Ophthalmia neonatorum	37	3	9	0		35	4	5	0	
Pneumonia † ..	514	28	275	9	4	695	52	241	7	8
Poliomyelitis, acute:										
Paralytic ..	21	1	3	1	2	26	2	1	1	2
Non-paralytic	6	0				11	1			
Puerperal fever § ..	205	25	15	1		246	49	5	0	1
Scarlet fever ..	964	66	62	17	28	822	50	59	37	33
Tuberculosis:										
Respiratory ..	485	47	152	20		593	88	97	16	
Non-respiratory	62	2	9	3		73	6	17	2	
Whooping-cough ..	587	25	38	3	10	2,932	2034	268	10	21

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery ..	1	0		0			0	0	0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	1	0	0	0			1	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	0	0	0		0	2	0	0
Influenza	69	4	6	0	1		2	0	0	0
Measles		0	0	0	0		1	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia ..	704	56	35	13	6		38	0	6	8
Poliomyelitis, acute	1	0		1	0		1			0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	110	10	8	4	0		9	7	0	3
Non-respiratory		0	1	0	0		1	1	0	1
Whooping-cough ..	0	0	0	0	0		0	2	0	0
Deaths 0–1 year ..	312	17	31	8	11		24	41	8	12
Deaths (excluding stillbirths) ..	12,003	917	749	164	201		767	613	119	186
LIVE BIRTHS ..	15,647	1218	1071	231	363		1282	1028	222	386
STILLBIRTHS ..	316	21	15				22	30		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Lister Festival Dinner.—The Royal College of Surgeons held their Lister festival dinner on March 28, with the president, Sir JAMES PATERSON ROSS, in the chair. Proposing the toast of "The College," Lord CROOKSHANK said that the College was one of the great links with the Commonwealth all over the world. It was of the greatest importance that professional people like themselves should let the world know what they were doing, for they were one of the channels by which the British race could show what it could achieve. Replying, Sir JAMES PATERSON ROSS outlined what the College was doing. They were having to rebuild, and they all looked forward to the establishment of the museum, which would house the Hunterian Collection and form the heart of the College. It was an enormous undertaking and something which they could not carry through unaided, but they were fortunate in having many friends who believed in their cause and to whom they were deeply indebted for encouragement. It had been said that they were over-ambitious, and that it was for that reason they had to appeal to their friends for help. The answer to that lay in their history and heritage. The prestige of the College was such that there was no need for it to build merely for self-enhancement. On the other hand, if they were to live up to their heritage they had to be prepared to shoulder their responsibilities, however onerous these might be. They believed they were doing no more than their plain duty to their students, their profession, and ultimately their patients. Sir ARCHIBALD MCINDOE toasted "The Lister Orator," Sir STEWART DUKE-ELDER responding. Sir RUSSELL BROCK then proposed "The Guests," and the president of the Royal Academy, Sir CHARLES WHEELER, replied. Many art schools, he said, had dispensed with anatomy, but at the Royal Academy they still believed in anatomy and had no faith in a human body with a hole through the centre of it—any more than surgeons would accept such a monstrosity.

Blood Transfusion in Scotland.—Since 1948–9 the demand for blood in Scotland has risen steadily from about 35,000 to over 110,000 bottles a year, according to the latest report (1956–7) of the Scottish National Blood Transfusion Association. Nor is there any sign of slackening in the rate at which the demand is increasing. By contrast, during the year ended March 31, 1957, the size of the donor panel fell by 2,445 to 132,740. Commenting on this situation, the Transfusion Association writes: "It may be doubted whether the use of blood to such an extent is absolutely essential or desirable, and the variation in consumption from region to region and hospital to hospital does suggest that economies in its use could be practised."

"Notes on Transfusion."—A revised edition of *Notes on Transfusion* has now appeared. This booklet, like its predecessors, has been prepared by the Ministry of Health's committee of regional transfusion directors, and is issued by the Ministry and the Department of Health for Scotland on behalf of the two national Blood Transfusion Services. It is intended primarily for use by medical staff of hospitals. In its 23 pages the *Notes* deals with choice and storage of transfusion fluids, blood grouping and the Rh factor, the technique of transfusion, untoward reactions, and the keeping of records.

Television Series Blamed.—After an inquest at Havant on a woman of 38 found with her head in a gas oven, her husband said that she had been very upset since seeing the programme on cancer in the B.B.C.'s television series *Your Life in Their Hands*. The inquest was on March 31. The husband stated in evidence that his wife was worried in case she had cancer; she had previously worried about her eyes, and twice threatened to take her life. At necropsy there was no evidence of disease of any sort. The coroner's verdict was: "Carbon monoxide poisoning, self-administered while the balance of mind was disturbed."

Gift for Liverpool Cancer Scheme.—The "Friends of Liverpool Radium Institute" Cancer Research Fund has promised Liverpool University £50,000, subject to the satisfactory conclusion of certain legal formalities. The money is to establish an endocrine unit in the university department of pathology (Professor H. L. SHEEHAN) and associated hospitals, for a long-term study of endocrine factors in certain types of cancer. It is proposed, as soon as possible, to establish a special laboratory for carrying out hormone assays, etc., and to appoint research staff.

Doctors' Cars in Central London.—The Metropolitan Police Office has offered through the B.M.A. the following advice to doctors practising in Central London: When a car is left parked on the highway it would help the police if a small notice could be displayed indicating where the driver can be found. It is suggested that a card approximately 3 in. by 3 in. should be fixed on the inside of the windscreen close to the road-fund licence, bearing a statement of the following kind: "Dr. —— is at present at No. —— Street." When a combination of traffic difficulties and urgency causes a doctor to park in an unorthodox way, such a procedure will enable the police to contact him should it be thought necessary to move his car. The Metropolitan Police Office hopes that in this way it will be possible to avoid a recurrence of those cases where the police have had to remove doctors' cars the drivers of which could not be identified or located. It stresses, however, that when a car is parked in a particularly obstructive or dangerous position—as, for example, on a pedestrian crossing—the police may well be obliged to remove it without waiting to refer to the driver.

Foundations' Fund for Research in Psychiatry.—This Fund offers a limited number of block grants to psychiatric departments with a view to stimulating research and the training of investigators. The grants are expected to range between $3,000 and $12,000 a year, and will be awarded for periods up to five years. The programme has been made possible by an award from the Ford Foundation. The closing date for applications for next year's grants is March 1, 1959. Further details may be obtained from Dr. MAX M. LEVIN, Foundations' Fund for Research in Psychiatry, 251, Edwards Street, New Haven, 11, Connecticut.

Nutrition Fellowship.—The National Vitamin Foundation invites those holding the equivalent of a U.S. doctorate degree in medicine or a biological science who wish to train in nutrition to apply for a National Vitamin Foundation–Russell M. Wilder fellowship. The fellowship is for three years and pays the recipient $4,500 in the first year, $5,000 in the second, and $5,500 in the third year. It becomes effective in July or September, 1959. Application forms, which must be submitted by September 1, 1958, can be obtained from the National Vitamin Foundation, 149, East 78th Street, New York 21.

Professor F. E. Tylecote, emeritus professor of medicine, Manchester University, has been made a fellow of the Royal Society of Health.

COMING EVENTS

Cavendish Lecture.—Sir GORDON GORDON-TAYLOR will deliver the West London Medico-Chirurgical Society's Cavendish lecture at the Royal Society of Arts, John Adam Street, on April 16 at 8.30 p.m. His subject will be "On Tradition."

N.A.P.T. Church Services.—To be held in London and Edinburgh on April 20, and in Llandaff, Cardiff, on April 27. Orders of service may be obtained from N.A.P.T., Tavistock House North, Tavistock Square, London, W.C.1.

Postgraduate Course.—For N.H.S. principals and assistants (fully registered for three years), April 28 to May 10 at the Welsh National School of Medicine. Details from the secretary of the school, 34, Newport Road, Cardiff.

Indian Medical Association (Great Britain).—Annual dinner and dance, May 1, at the Cumberland Hotel, Marble Arch,

7.30 for 8 p.m. Professor ROBERT PLATT, P.R.C.P., will be the guest of honour. Details from the hon. secretary, 766, Great West Road, Osterley.

Naval Medical Compassionate Fund.—Meeting of subscribers, May 2 at 2.30 p.m. at the Medical Department of the Navy, Queen Anne's Mansions, London, S.W.1.

T.A. Medical Officers' Association.—Annual dinner, May 16, 7.30 for 8 p.m. at the H.Q. Mess, Royal Army Medical College, Millbank. Details from the honorary secretary, c/o Central R.A.M.C. Mess, T.A. Centre, 57A, Farringdon Road, London, E.C.1.

Croonian Lecture.—Professor P. B. MEDAWAR, F.R.S., will lecture at the Royal Society, May 22. His subject will be "The Homograft Reaction."

Leeuwenhoek Lecture.—Dr. D. KEILIN, F.R.S., will lecture at the Royal Society, June 19. His subject will be "The Problem of Anabiosis or Latent Life History and Current Concepts."

British Association of Paediatric Surgeons.—Annual meeting, July 23–25, in London. Details from Mr. R. B. ZACHARY, F.R.C.S., The Children's Hospital, Sheffield, 10.

NEW ISSUES

SPECIAL JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Venereal Diseases.—Issued quarterly (£3 annually). The new issue, Vol. 34, No. 1, includes:

FLUORESCENT ANTISERA IN THE DETECTION OF SEROLOGICAL VARIETIES OF *Trichomonas vaginalis*. M. G. McEntegart, C. S. Chadwick, and R. C. Nairn.
SEROLOGICAL ASPECTS OF *Trichomonas vaginalis*. G. Lanceley.
GONORRHOEA IN MANCHESTER. INCIDENCE OF REPEATED INFECTIONS. Leslie Watt.
TREATMENT OF EARLY SYPHILIS WITH PENICILLIN. R. R. Willcox, F. J. G. Jefferiss, and G. L. M. McElligott.
A PILOT SCHEME OF VENEREAL DISEASES CONTROL IN EAST AFRICA. William Laurie.
THE TREPONEMATOSES—OR TREPONEMATOSIS? Ellis Herndon Hudson.
ANTIBIOTIC QUARANTINE OF GONORRHOEA. I. EFFECT IN FEMALES. Ira Leo Schamberg, Alfred Kalodner, and John William Lentz.
GRANULOMA INGUINALE OF THE EPIDIDYMIS. J. R. Jannach.
GRANULOMA INGUINALE IN A JAMAICAN AND HIS WIFE. Jack Barrow.
STREPTOMYCIN RESISTANT GONORRHOEA. C. D. Alergant.
TRIAL OF SIGMAMYCIN IN NON-SPECIFIC URETHRITIS. J. K. Oates.
EPIDEMIOLOGY OF NON-SPECIFIC URETHRITIS. J. T. Boyd, G. W. Csonka, and J. K. Oates.
NON-SPECIFIC URETHRITIS. C. P. Handforth.
VENEREAL DISEASES IN ENGLAND AND WALES. EXTRACT FROM THE ANNUAL REPORT OF THE CHIEF MEDICAL OFFICER FOR THE YEAR 1956.
REITER'S SYNDROME IN FIRST COUSINS. R. S. Morton.
FURTHER TISSUE CULTURE STUDIES OF NON-GONOCOCCAL URETHRITIS AND REITER'S SYNDROME. Denys K. Ford.
ORAL TREATMENT OF TRICHOMONAL VAGINITIS WITH 2-ACETYLAMINO-5-NITROTHIAZOLE ("TRITHEON"). Eric M. C. Dunlop, Elliot Philipp, and John D. Watt.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, April 14

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—(1) 5.15 p.m., Mr. Rodney Smith: Pancreatitis. (2) 6.30 p.m., Mr. L. N. Pyrah: Urinary Diversion.

Tuesday, April 15

B.B.C. TELEVISION.—9.30 p.m., "Your Life in Their Hands," No. 10—Looking to the Future, from Llandough Hospital, Glamorgan.
BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. E. S. Stern: Figuring it Out—A Statistical Approach to Psycho-Pathology and Prognosis.
ILFORD MEDICAL SOCIETY.—At King George Hospital, 8.45 p.m., annual general practitioner clinical meeting to which members of the Stratford Division, B.M.A., are invited.
MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Crumpsall Hospital, 4 p.m., clinical meeting.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Dr. J. St. C. Elkington: Cerebral Vascular Disease in the Light of Modern Techniques.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Arnott Demonstration by Dr. R. McP. Livingston: The Human Embryo: The Development of Form.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—(1) 5.15 p.m., Sir Arthur Porritt: Non-malignant Conditions of the Breast. (2) 6.30 p.m., Mr. Ronald Furlong: Osteoarthritis of the Hip.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. F. Swann: Some Observations on Cerebral Arteriography.

Wednesday, April 16

NORTH WESTERN TUBERCULOSIS SOCIETY.—At Aintree Hospital, Liverpool, 3 p.m., subject: Bacteriology and Pathology of Resected Specimens of Tuberculous Lung Tissue and the Relationship of Findings to Previous Chemotherapy. To be introduced by Dr. F. Turnbull. Papers by Dr. J. R. Edge and Dr. D. Bottrill, and Dr. T. Wilson. A discussion will follow.
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Dr. John Kirklin: Surgical Treatment of Tetralogy of Fallot.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—(1) 5.15 p.m., Professor F. A. R. Stammers: Complications of Gastrectomy. (2) 6.30 p.m., Sir Harry Platt, Bt.: Congenital Dislocation of the Hip.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. A. H. Charles: Minor Female Ailments.
ROYAL SOCIETY OF HEALTH.—2.30 p.m., Dr. N. C. Wright, D.Sc., Ph.D., Changing Feeding Habits of the Nation.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Royal Society of Arts, 8.30 p.m., Cavendish Lecture by Sir Gordon Gordon-Taylor, K.B.E.: On Tradition.

Thursday, April 17

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Mackenzie Davidson Memorial Lecture by Professor Sölve Welin (Malmo): Modern Trends in Röntgendiagnosis of the Colon.
HILL END HOSPITAL MEDICAL SOCIETY.—8.45 p.m., Dr. F. P. Lee Lander: Asthma.
HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., Dr. Grantly Dick Read: Philosophy and Function.
INSTITUTE OF PSYCHIATRY.—5 p.m., public lecture by Professor A. B. Hollingshead (Yale University): Social Class and the Treatment of Mental Illness.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At London Jewish Hospital, 8.30 p.m., clinical meeting.
NORTH-EAST LONDON CLINICAL SOCIETY.—At Prince of Wales's General Hospital, Tottenham, N., 2.30 p.m., meeting.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Lumleian Lecture by Dr. J. St. C. Elkington: Cerebral Vascular Disease in the Light of Modern Techniques.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor A. G. Jessiman: Hypophysectomy in the Treatment of Breast Cancer.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.15 p.m., Professor C. A. Wells: Prostatic Obstruction.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: Postgraduate demonstration in psychiatry.

Friday, April 18

BRITISH INSTITUTE OF RADIOLOGY.—(1) 2 to 4.30 p.m., Radiobiology meeting. Short reports of work in progress. (2) 5.30 p.m., Dr. J. F. Loutit: Experimental Transmission of Leukaemia in the Mouse: Dr. H. B. Hewitt and Dr. C. W. Wilson: Observations Concerning the Eradication of Experimental Mouse Leukaemia Using Total-body Radiation.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. G. Scadding: Clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., clinical lecture by Mr. J. C. Hogg: Treatment of Frontal Sinusitis.
KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.
LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.30 for 8.45 p.m., Dr. R. G. Cochrane: Leprosy—Its Challenge and Hope.
●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—(1) 5.15 p.m., Mr. R. Guy Pulvertaft: Reconstructive Surgery of the Hand. (2) 6.30 p.m., Mr. Selwyn Taylor: Radioactive Isotopes as an Adjunct to Surgery.
YORKSHIRE FACULTY OF GENERAL PRACTITIONERS.—At Littlewood Hall, General Infirmary at Leeds, 8.30 p.m., Dr. S. T. Anning: Problems of Eczematous Dermatitis.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Caldwell.—On March 3, 1958, at Dudley Road Hospital, Birmingham, to Isabel, wife of Dr. W. G. D. Caldwell, a son.

MARRIAGES

Hay—Bell.—On February 22, 1958, at St. Andrew's College Memorial Chapel, Christchurch, New Zealand, David Russell Hay, M.R.C.P., M.R.A.C.P., of 235, Antigua Street, Christchurch, to Jocelyn Valerie Bell, M.B., Ch.B., of 9, Holmwood Road, Christchurch.

DEATHS

Alderton.—On March 30, 1958, Charles Henry Arthur Alderton, L.R.C.P. & S.Ed., L.R.F.P.S., D.P.H., of 102, Highgate West Hill, London, N., aged 81.
Allan.—On March 28, 1958, at 4, Blackburn Place, Ayr, John Gibson Allan, M.B., Ch.B., formerly of Catrine, Ayr.
Birtwhistle.—On March 30, 1958, in hospital, Frederick Percy Hewetson Birtwhistle, M.D., J.P., of Barton-on-Humber, Lincs., aged 75.
Bradley.—On March 22, 1958, Edwin John Bradley, *M.C.*, M.D., F.R.C.S.Ed., of 26, Brackendale Road, Bournemouth, Hants, aged 67.
Campbell.—On March 22, 1958, at Kintail, Penshurst, Tonbridge, Kent, William Robert Caldwell Campbell, M.B., Ch.B., late of Inverallan, Helensburgh, Dumbartonshire, and Graingerville North, Newcastle.
Frazier.—On March 22, 1958, at Kuala Lumpur, Malaya, Alison Mary Frazier (formerly Richardson), M.B., B.Chir., D.Obst.R.C.O.G., aged 32.
Graff.—On March 20, 1958, Robert Archer Graff, M.R.C.S., L.R.C.P., Surgeon Captain, R.N., aged 55.
Griffith.—On March 21, 1958, Herbert Stuart Griffith, M.R.C.S., L.R.C.P., D.P.H., of 94, Wynn Road, Wolverhampton, Staffs, late of Sheerness, Kent.
Kelleher.—On March 25, 1958, at 58, Croydon Road, Penge, London, S.E., Timothy John Kelleher, M.B., B.Ch.
Laing.—On March 21, 1958, in Canada, the result of an accident, Robert Alistair Laing, M.B., Ch.B., Squadron Leader, R.C.A.F., of 3016, St. Therese Road, Fort Chambly, Quebec, aged 36.
Lowson.—On March 17, 1958, at Torquay, Victoria, Australia, Winifred Norah Doggart Lowson, M.B., Ch.B., formerly of Malaya.
Nimmo.—On March 19, 1958, at Westfield, Hathersage, Derbyshire, Arthur Ferguson Nimmo, M.B., Ch.B., of Attercliffe, Sheffield, aged 73.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Radioactive Phosphorus in Polycythaemia Vera

Q.—*Is radioactive phosphorus proving of value in the treatment of polycythaemia vera?*

A.—Treatment with radioactive phosphorus (^{32}P) is generally considered to be the most effective method of treating polycythaemia vera. It is, however, palliative rather than curative. The phosphorus is administered intravenously in single doses of about 5 millicuries, and it is usual to keep the patient in hospital for 4 days after this, as the urine will temporarily contain appreciable amounts of radioactive material. The majority of patients will respond favourably over the next 2–3 months: the platelet and leucocyte counts tend to fall first and the red-cell count and haemoglobin more slowly subsequently. Clinical improvement often antedates the haematological changes. The blood picture may become normal or almost normal and may remain so for 6–12 months or even longer. Relapse, however, is inevitable and the patient will probably require more radioactive phosphorus 6 to 24 months after the original dose. Such further treatments are usually followed by satisfactory responses.

It is possible that ^{32}P therapy increases the risk of transformation of polycythaemia to leukaemia. The degree of this risk is uncertain, but in any case it has to be balanced against the risk of serious complications, such as thrombosis, which develop in untreated or ineffectively treated patients.

Rh Assessment Early in Pregnancy

Q.—*What is the purpose of assessing the titre of Rh antibodies in the first trimester of pregnancy in women known to be Rh-negative?*

A.—If Rh antibody is found early in pregnancy the mother can be given plenty of warning that she will have to have her baby in hospital, and there will be time to make the necessary arrangements. A second reason for making the test early in pregnancy is that it may help in the interpretation of tests made later. Thus, if a test made in the last few weeks shows that Rh antibody is present, and it is known that antibody was absent at the beginning of pregnancy, it is virtually certain that the foetus is Rh-positive. When the husband is heterozygous for the Rh factor, evidence that the foetus is Rh-positive may be important.

Antibiotic Antagonism

Q.—*Has penicillin a "biological" antagonism to chlortetracycline, oxytetracycline, and other tetracyclines?*

A.—It would be more true to say that the tetracyclines are capable in certain circumstances of antagonizing the action of penicillin. The explanation of this effect is as follows. Penicillin is a bactericidal antibiotic, but a condition necessary for its action is that the bacteria shall be multiplying. The tetracyclines and chloramphenicol are bacteriostatic—that is, they act mainly by preventing multiplication, and thus remove the condition necessary for the killing action of penicillin. That this actually happens has been proved not only *in vitro* but in therapeutic tests in animals: in one of many such experiments by Jawetz and his colleagues[1] a dose of penicillin which when given alone saved 100% of mice from streptococcal infection saved only 45% when oxytetracycline was given in addition to it. The only clear example of such antagonism reported from the clinical field is in the treatment of pneumococcal meningitis. M. H. Lepper and H. F. Dowling[2] achieved a recovery rate of 70% in this infection by large and frequent doses of penicillin alone: when chlortetracycline was given in addition to the same doses of penicillin the recovery rate was only 21%. No intrathecal injections were given, and neither antibiotic can have attained a high concentration in the cerebrospinal fluid. The conditions were thus exactly suited for eliciting an antagonistic effect: in other tissues, where higher antibiotic concentrations are attained, its results may not be evident, because the action of the interfering antibiotic alone may suffice for cure. Nevertheless, this type of combination is probably better avoided unless there is some exceptional and explicit reason for using it.

REFERENCES
[1] Jawetz, E., and Speck, R. S., *Amer. J. med. Sci.*, 1952, **223**, 280.
[2] Lepper, M. H., and Dowling, H. F., *Arch. intern. Med.*, 1951, **88**, 489.

Albuminuria and Bacilluria

Q.—*Does the absence of albumin in a catheter specimen of urine render unnecessary any further investigations for bacterial infection?*

A.—No. The protein found in urine in the acute stage of an infection of the urinary tract is that of the inflammatory exudate. When the acute stage subsides, persistent inflammation is usually of low grade and the amount of protein escaping from capillaries in the tissues involved is often too small to be detectable when diluted in a large volume of urine. A chronic infection may indeed take the form of an almost pure bacilluria, with not even a marked excess of leucocytes in the urine.

The best simple test of whether an infection exists is to observe whether a fresh specimen is or is not perfectly clear. It should of course be collected with precautions against external contamination, and turbidity due to the presence of phosphates should be cleared by acidification.

Poliomyelitis Immunization

Q.—*What is the present state of knowledge on anti-poliomyelitis vaccination with regard to (1) number of injections required; (2) degree of immunity achieved; (3) duration of immunity; and (4) risks, if any?*

A.—(1) The recommended practice is to give two injections of 1 ml. of the poliomyelitis vaccine subcutaneously or intramuscularly, followed by a third injection 6–8 months later. (2) Serological examination of immunized children indicates that neutralizing antibodies against all three types of virus appear in the blood of immunized children. The levels against type 2 are particularly high. There is evidence that immunized children have a better chance of escaping paralytic poliomyelitis as compared with non-immunized children (about 5:1). (3) The duration of immunity is as yet difficult to determine, but it can be stated that it will last for at least two years. (4) There are scarcely any risks involved in immunization against poliomyelitis. Apart from casual reactions such as may follow inoculation with any antigen (slight fever, malaise for 10 to 24 hours), there are a few cases recorded of allergic reactions following poliomyelitis immunization owing to the presence of traces of antibiotics in the vaccine. So far no evidence has been recorded of sensitivity caused by marked kidney tissue or any adverse effect due to blood-group sensitization.

Brittle Finger-nails

Q.—*Can the constant use of blackboard chalk cause excessive brittleness of the finger-nails? Can anything be done to alleviate the condition?*

A.—It is unlikely that chalk is a cause of the brittle nails. Apart from industrial contact with chemicals and much household damage from the use of detergents and alkalis, brittleness of the nails reflects some disturbance of general health or tone.

Though much work has been done on the problem of brittle nails, the causative mechanism is not clear. It may well bear some relationship to chapping of the skin, which is chiefly due to cold and lack of moisture so that the horny

layer becomes dry and brittle. This can be counteracted by such things as glycerin. It is conceivable that chalk may be an aggravating factor by increasing dryness of skin and nails. In any case, it is likely that the protection afforded by the use of a nail varnish would be beneficial.

Daily "Drinamyl"

Q.—*Is it safe for a woman of 76 to take one tablet of drinamyl (dexamphetamine and amylobarbitone) daily over a long period?*

A.—One tablet of "drinamyl" contains 5 mg. of dexamphetamine and 32 mg. of amylobarbitone. It is difficult to envisage any harm arising from the daily administration of a single tablet. It would be advisable, however, to warn the patient against increasing the amount taken.

"Congenital" Syphilis

Q.—*Are congenital syphilis and inherited syphilis the same thing or separate entities?*

A.—In common usage the terms "congenital syphilis" and "inherited syphilis" mean the same thing. In fact "congenital" implies merely that the disease was present at birth[1]—e.g., congenital dislocation of the hip—whereas "inherited" means that the disease has been inherited from the parents, which is not strictly true. What happens, of course, is that the foetus becomes infected (from its mother via an infected placenta) after its intrauterine life has commenced. Fournier[2] used the word "inherited" in those cases in which he considered infection to have taken place at the moment of conception. This is now thought not to occur. The word "prenatal" is to be preferred. It indicates unequivocally that infection took place some time before birth.

REFERENCES

[1] Nabarro, D., *Congenital Syphilis*, 1954. Arnold, London.
[2] Fournier, E., *Stigmates dystrophiques de l'Hérédo-Syphilis*, 1898. Paris.

Side-effects with Glutethimide

Q.—*Have any side-effects been reported with glutethimide?*

A.—The commonest side-effect is undoubtedly skin rashes. It is difficult to obtain accurate information on their frequency, but they certainly occur in under 10% of patients to whom the drug is given, and the incidence is probably much less than this. I am unaware of any reported case of agranulocytosis, and no one has been able to direct me to any reference reporting this condition, nor have I heard of it on talking with colleagues. Dryness of the mouth is apparently a common complaint. It is not clear how this develops and it only causes a minor degree of discomfort. I have no information about any other side-effects associated with glutethimide.

Frischzell Therapy

Q.—*What is Frischzell therapy? Is it of use in intermittent claudication?*

A.—Dr. Niehans, of Switzerland, introduced Frischzell therapy approximately 15 years ago as a method of treatment for nearly all chronic diseases, and he considered it was particularly valuable in the management of patients with atherosclerosis, chronic renal disease, osteoarthritis, rheumatoid arthritis, and chronic gastric and duodenal ulcers. The basis of the treatment is that fresh extracts of the pituitary and other endocrine glands from newborn calves are mixed in saline and injected into the patient. Dr. Niehans has written a large number of papers on this subject.

The word Frischzell means fresh cell. More recently the cells have not been administered fresh but after the process of freeze-drying, when the product is called Siccacel or dry cell. Again, these dry cells are stated to be effective in nearly all chronic diseases. This method of treatment appears to be a modification of that introduced in 1933 by Filatov, of the U.S.S.R., who considered that "any tissue taken from man or animal when isolated from the body and stored in unfavourable but not lethal conditions undergoes biochemical readjustment and produces special substances which maintain the vital functions of this tissue. When introduced into a diseased body they in turn stimulate its vital functions, thus leading to its recovery."

It is apparent that treatments of this type which are sponsored as a cure for conditions as variable as atherosclerosis and chronic duodenal ulcer must be subjected to the strictest scrutiny before the claim can be accepted that they are effective in a treatment of a condition with such a tendency to spontaneous improvement as intermittent claudication due to peripheral arterial disease.

NOTES AND COMMENTS

Oral Hormones for Menstrual Disorders.—Mr. A. A. LOESER (London, W.1) writes: Would you allow me to make some comments about the so-called Swyer's regime for the regulation of menstrual cycles in menstrual disorders ("Any Questions?" March 8, p. 598)? . . . But no standard regime whatsoever is right in women with menorrhagia as long as a diagnostic premenstrual curettage has not been performed. It is a retrograde step in oral hormonal treatment to prescribe any hormone without knowing the exact premenstrual state of the endometrium. During an oral hormonal treatment repeated examination of the consistency of the uterus, the breast, and even of the thyroid gland is essential. Otherwise endocrine gynaecology becomes the paradise of non-competent doctors and may even be a danger to women in whose family cancer runs.

OUR EXPERT replies: Mr. Loeser is, of course, quite right in requiring that diagnosis should precede therapy. Limitation of space obviously prevented my referring to Swyer's paper[1] in detail, in the first paragraph of which Mr. Loeser will find: "Clearly the adoption of this attitude [i.e., the treatment of dysfunctional uterine bleeding as though it were a disease entity] presupposes the elimination by the appropriate methods of systemic or local disease which might itself give rise to the menstrual disorder in any particular case. . . . In the account which follows, it is to be understood that, except where specifically indicated, only disorders of function are under consideration, and that where underlying organic disease exists the correct treatment is that directed towards the care of the disease itself." The potential danger of carcinogenesis from oestrogen therapy is one of which we are all aware. Experimental evidence suggests that the danger is small or non-existent when *interrupted* oestrogen treatment is given, though real when the treatment is continuous. Convincing clinical studies do not seem to have been published.

REFERENCE

[1] Swyer, G. I. M., *Brit. med. J.*, 1950, **1**, 626.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

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